90-476

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CLERK

No. ____

IN THE

SUPREME COURT OF THE UNITED STATES

OCTOBER TERM, 1990

WYETH-AYERST LABORATORIES DIVISION
OF AMERICAN HOME PRODUCTS CORPORATION,

Petitioner,

v.

MICHELLE GRAHAM, an Infant under the age of 18 who sues by her Parents, Guardians and Next Friends, CHARLES GRAHAM AND TAMMY GRAHAM,

Respondent.

APPENDIX TO THE PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE TENTH CIRCUIT

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TABLE OF CONTENTS

Page

APPENDIX A (court of appeals decision dated June 25, 1990) 1a

APPENDIX B (district court decision on summary judgment dated July 22, 1987) 43a

APPENDIX C (district court verdict dated October 14, 1987) 78a

APPENDIX D (Brief for the United States as *Amicus Curiae* in the court of appeals dated June 30, 1988) 80a

APPENDIX E (Fifth Circuit opinion in *Hurley v. Lederle Laboratories,* as amended, dated January 5, 1989) 105a

APPENDIX F (statutes and regulations)

Statutes 119a

Regulations 168a

APPENDIX G (Program for Sixth International Symposium on Pertussis, September 26-28, 1990) 238a

APPENDIX A
906 F.2d 1399

FILED
United States Court of Appeals
Tenth Circuit
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ROBERT L. HOECKER
Clerk

PUBLISH

UNITED STATES COURT OF APPEALS
FOR THE TENTH CIRCUIT

MICHELLE GRAHAM, an
under the age of eighteen w
by her parents, guardians, a
Charles Graha
Jimmy Graham,

SION OF AMERICAN HOME
PRODUCTS CORPORATION,

Defendant-Appellant.

APPEAL FROM THE UNITED STATES DISTRICT
COURT FOR THE DISTRICT OF KANSAS,
Case No. 85-1481

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Marlys A. Marshall, Andrew W. Hutton of Michaud & Hutton of Wichita, Kansas, Attorneys for Appellee.

Before SEYMOUR, Circuit Judge, [illegible] Circuit Judge and GARTH, Circuit Judge.*

Garth, Circuit Judge.

This appeal arises as a result of a $4,000,000 verdict against Wyeth Laboratories (Wyeth), the manufacturer of a DTP vaccine. It presents us with a number of evidentiary and legal questions. The most significant of these are: (1) should judgment NOV have been granted to Wyeth? (2) Are state tort awards for the improper manufacture of vaccines preempted by federal regulation? (3) Does Kansas allow for tort awards based upon strict liability or the negligent manufacture of an "inherently unsafe" vaccine? (4) Were a number of Wyeth's experts improperly excluded from testifying at the trial? (5) What is the correct procedure for the use, redaction and admission of "learned treatises" as evidence under Fed. R. Ev. 803(18)? And (6) was Wyeth

* The Honorable Leonard I. Garth, Senior United States Circuit Judge for the Third Circuit, sitting by designation.

entitled to post-judgment relief when one of Graham's experts recanted much of his testimony in subsequent court proceedings? Other less significant allegations of error have also been raised, and will be addressed in the course of this opinion.[1]

Our standard of review in reviewing a denial of motion for judgment NOV has been prescribed as follows:

> [The standard for determining whether to grant a judgment N.O.V., as for a directed] whether there is literally no evidence [party opposing the motion, but evidence upon which the jury] verdict for that party. The court [may not weigh the evidence, pass on the credibility] of witnesses, or substitute its judgment for that of the jury. Rather, it must view the evidence most favorably to the party against whom the motion is made and give that party the benefit of all reasonable inferences from the evidence. On appeal, we employ the same standard of review as does the trial court.

Brown v. McGraw, 736 F.2d 609, 612-13, (10th Cir. 1984).

On the other hand, we test the various individual evidentiary rulings made by the district court and the denial of Wyeth's Fed.R.Civ. Pro. 60(b) motions, for an "abuse of discretion"; see *In re International Coating*

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1. One additional issue raised was whether one of Graham's counsel should be disqualified based on a conflict of interest. That issue will not be addressed here. At oral argument, we ruled that the conflict precluded representation of Graham by the firm of Michaud & Hutton of Wichita, Kansas. We announced that our ruling would [be the subject of an opinion to be filed. Oral argument was then] presented by [illegible] attorney Marshalsky, of Wat[illegible] of Milwaukee,

Applicators, 647 F.2d 121, 124 (10th Cir. 1981). On issues related to interpreting federal law the standard of our review is plenary, and on interpreting Kansas law we give some deference to the district court's interpretation, but review is ultimately *de novo*. See *Wilson v. Al McCord Inc.*, 858 F.2d 1469, 1473 (10th Cir. 1988) ("The issue for our consideration is the trial judges legal interpretation of state law to which we give some deference but ultimately review *de novo*.")

We will affirm the denial of judgment NOV, reverse the denial of the motion for a new trial, and remand to the district court for a new trial on all issues. Additionally, we will reverse the district court's denial of Wyeth's Fed.R.Civ. Pro. 60(b) motion for post-judgment relief. Inasmuch as we are ordering a new trial on all issues, we assume that the subject matter of Wyeth's 60(b) motion will find expression during that proceeding.

I.

A.

This appeal originated from a $15,000,000 jury verdict in favor of Michelle Graham ("Graham") and against Wyeth for the defective manufacture of Wyeth's DTP vaccine. Wyeth manufactured a DTP vaccine which is used to immunize children against the diseases of diphtheria, tetanus (lockjaw) and pertussis (whooping cough). The vaccine is administered to infants at two, four, six and eighteen months. A booster injection is administered prior to the child's entrance into school.

The DTP vaccine is comprised of three component parts, diphtheria toxoids, tetanus toxoids, and a pertussis whole cell vaccine. It is the pertussis component of the vaccine that is the subject of this litigation and which allegedly caused the severe reaction suffered by Graham. While Graham contends that the pertussis component of this vaccine could have been safer, and

that in fact safer versions of the vaccine are available, she does not argue that a pertussis vaccine is generally unnecessary or that it has not saved thousands of lives.[2]

The DTP vaccine containing the "whole cell" pertussis vaccine was licensed by the FDA in 1949. Due to the widespread use of the vaccine in this country, pertussis has virtually been eradicated. However, because of the persistent nature of the pertussis bacterium, there is a continuing and substantial risk of epidemics if the use of the vaccine was to be discontinued or was to decline significantly, and in fact epidemics have occurred in countries that have eliminated the pertussis vaccine from their list of mandatory vaccines.[3]

The nature of the DTP vaccine and its component parts was recently described by the Ninth Circuit as follows:

> By introducing an antigenic factor into the body, vaccines stimulate the production of antibodies that protect against disease. Some infectious organisms, such as those causing diphtheria and tetanus, excrete soluble toxine insolable [sic] by medical research. The toxin is inactivated with formaldehyde and transformed into a toxoid. The toxoid is then used in a vaccine, as it can immunize against

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2. In the early 1900's, pertussis was a leading cause of death in children in this country. In 1934, when this country suffered its worst pertussis epidemic, there were 265,000 reported cases of pertussis that year, and 7500 related deaths. By the early 1940's, pertussis was responsible for two and one-half times the number of deaths as all of the following diseases combined: measles, mumps, rubella, diphtheria, polio, meningitis, chicken pox, and scarlet fever. See Minman and Koplan, *Pertussis and Pertussis Vaccine: Re-Analysis of Benefits, Risks and Costs,* 251 Journal of the American Medical Association (JAMA) 3109 (June 15, 1984).

3. For an extensive comparison of the various countries' practices, and the epidemiological results, see *Loveday v. Renton,* (Queens Bench, England) March 31, 1988 (available on Lexis, No. 1982 L 1812).

> disease by stimulating the production of antibodies in the recipient, even though it has lost its own poisonous qualities.
>
> This is not the case, however, with [the pertussis component]. [The pertussis vaccine] is a so-called whole cell vaccine because it contains whole killed pertussis organisms. The whole organism is used because the pertussis organism contains fifteen or sixteen different antigens, and medical science has yet to isolate the one that stimulates protection against the disease.

Toner v. Lederle Laboratories, 779 F.2d 1429, 1430 (9th Cir. 1986).

Because the whole cell vaccine retains the poisonous qualities, it is neurotoxic and can cause adverse reactions which may be mild or severe. Mild reactions may include swelling, fever, irritability, and crying spells. Severe reactions can perhaps include encephalopathy,[4] paralysis and death. In recognition of the dangerous propensities of the whole cell vaccine, efforts have been made to develop a fractionated cell pertussis vaccine without any of the harmful toxoids. During the 1950's, the Eli Lilly Company developed a "split cell" vaccine called Tri-Solgen. Early studies indicated a fractionated vaccine was less toxic than the whole cell and it was approved by the FDA in 1967. At that time, Lilly occupied a substantial share of the DTP market. In 1975, Lilly withdrew from the vaccine business and sold its Tri-Solgen vaccine to Wyeth. According to Graham, in an effort to save on cost, Wyeth substituted its own "ingredients" (or "strains") into the Lilly "recipe" for the split cell vaccine. Wyeth then attempted to license this vaccine, but no license was granted by the FDA. Wyeth has made no further attempts to license a

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4. "Any disease of the brain", Stedman's Medical dictionary, 5th ed. (1982).

fractionated cell vaccine and no such vaccine is licensed in this country[5] today. Moreover, pharmaceutical companies are prohibited from marketing a product absent a license — to do so would constitute a criminal offense; (21 U.S.C. §§ 331(d), 333(a), 355(a)).

B.

This lawsuit had its origins in the tragic history of the plaintiff, Michelle Graham, a child who has suffered, and is suffering from brain damage, and who requires continuous treatment and care. Michelle Graham (by her parents) alleged that she sustained severe and irreversible brain damage after being vaccinated against diphtheria, pertussis and tetanus with a defective vaccine produced by Wyeth.

On March 17, 1980, Michelle Graham, who was only a few months old, was administered Wyeth's DTP vaccine by a nurse at a county office of the Missouri Department of Health. Shortly thereafter Graham was diagnosed as having suffered from a severe and irreversible neurological condition known as encephalopathy which caused retardation and prevents Graham from ever leading a normal life. Graham sued Wyeth alleging that its DTP vaccine caused the brain damage, and that this type of injury could have been avoided if only Wyeth had used more care in controlling the level of toxoid in its vaccine. Wyeth denied that its DTP vaccine did in fact cause Graham's brain damage, or that the DTP vaccine even could, in fact, cause this particular type of damage. Wyeth additionally maintained that, as a matter of law, it could not be liable even if the vaccine did cause Graham's injury because, vaccines, under applicable

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5. Japanese companies have developed and are currently using a pertussis toxoid (i.e., acellular) vaccine. This vaccine is purported to be as efficacious as the whole cell vaccine, but far less reactive. There appear to be some problems with the acellular vaccine as well, see *Loveday*, supra note 2, at 43-47.

Kansas[6] law, are to be treated as inherently dangerous products and thus the vaccine manufacturers are deemed immune from liability.[7]

The district court determined according to Kansas law[8] that Graham could proceed on its negligence theories. In the district court's summary judgment opinion, however, it held for Wyeth, and against Graham, on the strict liability "warning" issue. On Graham's "design defect" strict liability claim, the court determined that there was an issue of material fact as to whether the vaccine was "unavoidably unsafe" within the meaning of Restatement of Torts §402A comment (k) thereby precluding summary judgment for Wyeth on its comment (k) defense. The court therefore permitted Graham to seek to establish that Wyeth's vaccine was "avoidably unsafe"; see infra p. 13-16.

After more than seven weeks of trial during which numerous experts testified as to causality, and others were excluded from testifying, the jury returned a verdict in favor of Graham for $15,000,000 in compensatory damages. Motions for judgment notwithstanding the verdict and for a new trial based on evidentiary errors were made by Wyeth and denied by the district court. Wyeth appealed. Thereafter, Wyeth, claiming to have discovered new evidence after its notice of appeal was filed, brought two Fed. R.Civ.Pro 60(b) motions in the

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6. Both parties stipulated that Kansas law applied to this case, which was brought pursuant to our diversity jurisdiction, 28 USC §1332; *Graham v. Wyeth Laboratories*, 666 F.Supp. 1483, 1485 (D. Kan. 1987).

7. As a general matter, Kansas subscribes to the principles of strict (products) liability for manufactured goods; see *Brooks v. Dietz*, 218 Kan. 698, 699-703, 545 P.2d 1104 (1976) and *Note. Strict Liability in Tort Adopted in Kansas*, 25 Kan.L.Rev. 462 (1977). This court in *Symons v. Mueller Co.*, 493 F.2d 972 (10th Cir. 1974) forecast that Kansas would adopt such a rule.

8. See *Graham v. Wyeth Laboratories*, 666 F.Supp. 1483, 1484-85 (D. Kansas 1987) for the district court's analysis of all the pre-trial issues.

district court for relief from the judgment and for a new trial. Those motions were denied by the district court, and an appeal from those denials was taken as well.

II.

We turn first to Wyeth's contention that the district court erred in denying Wyeth's action for judgment N.O.V. As we have observed, the appropriate standard to be satisfied for a judgment notwithstanding the verdict where proofs are at issue is "whether there is evidence upon which the jury could properly find a verdict for" the non-moving party, *Brown v. McGraw*, 736 F.2d 609, 612-13, (10th Cir. 1984) – in this case, Graham.

Wyeth contended that no evidence which would prove a causal relationship between the DTP vaccine and Graham's injury was adduced. Wyeth focused on Graham's hypothesis that the whole call DTP vaccine contains two components (endotoxin and pertussis toxin) which can cause retardation, and argued that no such proofs appear of record.

Because of the critical significance of a causal connection between the DTP vaccine and Graham's injury – a connection bitterly disputed by the parties – we requested additional briefing on this issue. We were thereupon directed to Graham's evidence that at birth, Graham was normal (Tr. 1416-1422); that she experienced no health problems prior to her vaccination (Tr. 2028-2034); that Dr. Gilmartin, a pediatric neurologist, testified that Graham's retardation was caused by the DTP vaccine (Tr. 1570, 1573)); that Dr. Gilmartin did not believe her injury was due to a stroke occurring prior to her vaccination (Tr. 1587-1588, 1619); that endotoxin can injure blood vessels from the inside out (Dr. Zahalsky) (Tr. 302-307, 313-320); and that endotoxins can cause stroke (Dr. Guggenheim) (Tr. 3801-3803, 3870-3877).

Wyeth, which claimed among other theories, that Graham had suffered a stroke *prior to her vaccination* and that it was the pre-vaccination stroke which resulted in her disability, took issue with each of Graham's experts and with the evidence of causation. However, in ruling on a motion for judgment N.O.V., the district court and this court, are precluded from weighing the evidence, passing on the credibility of witnesses, or substituting a court's judgment for that of the jury. *Yazze v. Sullivent*, 561 F.2d 183, 188 (10th Cir. 1977). Thus, the fact that Wyeth alleged that the evidence of causation was misconceived and that examined properly, the evidence would result in a finding of no causal connection between the DTP vaccine and Graham's injury, is of no relevance. Viewing, as we must, the evidence most favorably to the party against whom the motion was made – here, Graham – and giving Graham the benefit of all reasonable inferences, we are satisfied that the district court did not err in denying Wyeth's motion for judgment N.O.V. addressed to causation.

Wyeth also moved for judgment N.O.V., relying essentially, among other grounds, on various theories of law and the failure of Graham's evidence to meet her requisite burden of proof. Wyeth claimed that Graham's design defect theory was barred as a matter of law, and was unsupported by the evidence; that Graham's claims of inadequate warning based upon negligence were legally insufficient and not supported by evidence; and that Graham's claims were preempted by federal law.

Although our review of motions for judgment NOV relating to evidentiary errors is to determine whether there is any evidence on the record, our review of a district court's legal conclusions is plenary. We are in agreement with the district court's legal analysis of

Wyeth's preemption claim,[9] and its determination that Wyeth's defense of adequate warning was a jury function. *See Graham v. Wyeth Laboratories*, 666 F. Supp. 1483, 1488 (pre-emption), 1494 (application of Kansas law), 1498 (adequacy of warning), (D. Kan. 1987).

We recognize, of course, that the district court opinion was written in response to Wyeth's motion for summary judgment. However, the same legal principles and arguments with which the district court treated, albeit in a summary judgment context, have now been advanced by Wyeth on appeal as grounds for reversing the district court's ruling which denied Wyeth's motion for judgment N.O.V. Because our reading of the record and our analysis of the relevant authorities cited by the parties and the district court are in accord with the conclusions reached by the district court in its summary judgment opinion and with its denial of Wyeth's motions, we do not deem it necessary to discuss these issues (other than Wyeth's §402A comment (k) defense to Graham's "design defect" claim) in any greater detail than the district court discussed them in its opinion. And, to the extent that Wyeth put in issue the proofs adduced with respect to each legal ground advanced, our independent review of the record satisfies us that judgment NOV in favor of Wyeth should not have issued.

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9. We note that since the district court correctly analyzed the pre-emption issue, two State Supreme Courts and two Federal Courts of Appeal have addressed this issue as well. Each has determined that pre-emption does not apply. See *Abbot v. American Cyanamid*, 844 F.2d 1108 (4th Cir. 1988); *Hurley v. Lederle*, 863 F.2d 1173 (5th Cir. 1988); *White v. Wyeth Laboratories, Inc.*, 533 N.E.2d 748 (Ohio 1988) and *Shackil v. Lederle Laboratories*, 561 A.2d 511 (N.J. 1989). We agree with their rulings that federal pre-emption does not prevent state tort law awards arising from improperly manufactured drugs or vaccines, even in situations where the drugs or vaccines have met the FDA's minimum standards for licensing.

With respect to Wyeth's §402A Comment (k) defense the Kansas Supreme Court has recently addressed this issue in *Johnson v. American Cyanamid*, 718 F.2d 1318 (Kan. 1986) and, as this court's jurisdiction is based on diversity, the pronouncements of that tribunal bind us on this issue. Under the guidance of *Johnson* we are satisfied, as was the district court, that Kansas has accepted comment (k) as the law. The rationale underlying comment (k) is that since the manufacturer is using the best technology available to it in order to produce a product that under current technology is "inherently dangerous" (*i.e.* "unavoidably unsafe") we should not hold the manufacturer strictly liable for any injury that may result. The over-arching goal of strict liability is to force manufacturers to lessen, if not eliminate, the danger of their products. The comment (k) exemption is granted in the case of "inherently dangerous" products since it is assumed that the products cannot be improved: thus no liability should attach.

Wyeth claimed that because its DTP vaccine was "unavoidably unsafe", it could not be held liable on a strict liability "design defect" theory. In its opinion denying summary judgment to Wyeth on this claim, the district court determined that a material dispute of fact existed as to whether the DTP vaccine produced by Wyeth was "unavoidably unsafe". The district court referred to an affidavit by Dr. Zahalsky, one of Graham's experts, which asserted that Wyeth had the capability to produce a safer vaccine. Hence the question was presented as to whether the "unsafety" of the vaccine produced by Wyeth was "unavoidable."

The district court read *Johnson* to require a determination at the outset as to whether the vaccine was "unavoidably unsafe". The district court found that a material dispute of fact precluded that determination at the summary judgment stage. Applying *Johnson* to such

a circumstance,[10] the district court then permitted Graham to proceed on a "design defect" theory, both as to negligence and strict liability, stating:

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10. *Johnson v. American Cyanamid*, 718 F.2d 1318, 1323 (1986) states unequivocally that "The trial judge should have heard the evidence on the [unavoidably unsafe product] issue outside the presence of the jury and made the determination thereon."

Despite this statement the Kansas Supreme Court in *Johnson* did not remand the §402A comment (k) issue for a factual determination. Instead the court determined as a matter of law that the vaccine in question was an "unavoidably unsafe" product and thus subject to a §402A comment (k) defense.

As we indicate in text, the district court, finding a material dispute of fact with respect to the issue of unavoidable "unsafety", delayed ruling on this issue until mid-trial, when the court struck Wyeth's §402A comment (k) defense. We cannot say that the district court abused its discretion in declining to hold a "mini-trial" prior to trial limited to the issue of "unavoidable unsafety." See *Moe v. Avione Marcel Dassault-Brequet Aviation*, 727 F.2d 917, 935 (10th Cir. 1987) (Although arising in a different context, this Court, among other things, stated: mini-trials can result in "undue delay, waste of time, and needless presentation of cumulative evidence").

Wyeth argued below and reasserts here that the comment (k) defense, if successful, also precluded a design defect negligence action. We disagree. Exempting manufacturers from strict liability clearly differs from exempting them from negligence liability. In *Johnson*, 718 P.2d at 1319, the Kansas Supreme Court made clear in its first syllabus that a plaintiff may proceed on a theory of negligent design defect where she is prohibited by comment (k) from proceeding on a strict liability design defect theory.

This is as well the position taken by the California Supreme Court in its most recent discussion of this issue. In *Brown v. Superior Court*, 751 P.2d 470, 482, n.12 (Cal. 1988) the Court stated:

> Our conclusion [that drug manufacturers are not strictly liable for the damage their product causes] does not mean, of course, that drug manufacturers are free of all liability for defective drugs. *They are subject to liability for manufacturing defects, as well as under general principles of negligence* and for failure to warn of known, or reasonable knowable side effects.

(Emphasis added.)

> [C]omment k's application does not shield the seller of a product from negligence claims. Such a result fits within the policy of comment (k) — *i.e.,* by denying plaintiffs recovery based on finding the manufacturer strictly liable if the drug is dangerous, and requiring the plaintiff to prove negligence, the policy of encouraging the production and marketing of safe, useful products is furthered.
>
> Of course, the inquiry into whether a manufacturer acted negligently is, in a general sense, similar to the comment k inquiry of whether a drug is unavoidably unsafe. Thus, in a case such as this where both theories (strict liability and negligence) are asserted, the evidence from which the court must determine if the product is unavoidably unsafe need not be heard outside the presence of the jury as it will be the same evidence from which the jury will determine negligence.

666 F.Supp at 1498 (citations omitted).

At a subsequent hearing during trial, the district court struck Wyeth's §402A comment (k) defense, as the district court found that it was not an available defense to Wyeth in light of the proofs developed at trial. Wyeth contends we should construe *Johnson* to hold that the comment (k) defense precludes a strict liability design defect claim as a matter of law in all cases involving licensed prescription vaccines. Other state Supreme Courts are divided on how to address comment (k) defenses. Compare *Brown v. Superior Court*, 751 P.2d 470, 481-83 (Cal. 1988) with *Toner v. Lederle Laboratories*, 732 P.2d 297, 3050309 (Idaho 1987). We view the *Johnson* opinion as unclear on this issue. Given the range of views of other state courts, *see generally, Note. A Prescription for Applying Strict Liability: Not all Drugs Deserve Comment K Immunization,* 21 Ariz. St. L. J. 809, 819-20 (1989), we are not inclined to disturb the district court's interpretation of Kansas law.

In view of these rulings, and particularly its summary judgment determination, we construe the jury's response to the "design defect" interrogatory as well as to the negligence charge[11] as having its roots in the same evidence: that is, that Wyeth's vaccine would have been safer if the level of endotoxin had been reduced — a subject to which we refer in section V, *infra*.[12] Thus, the jury's affirmative answer to interrogatory 4 ("design defect") must be read as a jury finding that Wyeth's vaccine was "avoidably," and not "unavoidably," unsafe and that a reduction of endotoxin levels was technologically feasible.

We have also considered the other errors asserted by Wyeth, in connection with the district court's charge. Because we are ordering a new trial, we do not find it necessary to discuss or rule on the errors which Wyeth claims, over its objections, were committed by the district court judge. This is particularly so, because it is unlikely that the same errors will occur again on retrial, and we are confident that Wyeth will have an opportunity to address itself to any such new instructions that will be given at a new trial.

III.

Wyeth raises numerous issues as grounds for the granting of a new trial, and we find many of them persuasive. In particular we conclude that numerous evidentiary errors occurred at trial and were of such a degree as to mandate a new trial.

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11. Special verdict form question 3 asked:

3. In March of 1980, was defendant Wyeth negligent in connection with testing, designing, and/or warning in regard to its DTP whole cell vaccine, which was the legal cause of plaintiff's injuries?

The jury answered "Yes."

12. In that action we refer to Wyeth's newly discovered evidence of miscalculation made by Graham's experts as to endotoxin levels.

A.

In our view, one of the most serious evidentiary errors committed at the trial was the exclusion of critical portions of Dr. Cibis' testimony. Dr. Cibis, a pediatric ophthalmologist who had treated Graham, was prepared to testify, and did so testify at deposition,[13] that Graham had suffered a stroke *before* her vaccination and that accordingly the DTP vaccine was not the cause of her disability. The essence of Dr. Cibis's testimony was that, in light of the CT scan which had been made available to him after his initial diagnosis of Graham, he would now attribute to an eye problem (Cogan's Apraxia), a clear manifestation of stroke. (Tr. 3974-81, 4002-4006). He originally, and without the benefit of a CT scan, diagnosed Graham's eye problem as minor. The thrust of his testimony would thus support Wyeth's contention that Graham had already suffered her stroke before she had been vaccinated, since Dr. Cibis' examination occurred before the DTP vaccine had been administered.

The district court prevented Dr. Cibis from so testifying, ruling that for any expert who testified as to causation the expert had to be knowledgeable about the workings, nature and medical literature concerning endotoxins. (Tr. 3924-26) This was error.

Dr. Cibis would have testified that the vaccine did *not* cause Graham's injury. The lack of knowledge by Dr. Cibis as to the workings or nature of DTP, his lack of expertise as to endotoxin, or his unfamiliarity with the course of this particular litigation, was not relevant to that testimony. To promulgate a rule that one must be an expert in DTP or endotoxin in order to testify as to that particular substances' effect may be perfectly reasonable; but to use such a criterion to exclude experts from testifying that the vaccine was *not* the cause of injury (because Graham had already suffered the stroke

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13. The deposition of Dr. Cibis took place the morning he testified. The district court judge attended parts of the deposition.

at the time of the original examination) had to remove from the jury significant evidence that Wyeth's vaccine was not responsible for Graham's condition.[14]

> As a general rule,
>
> to warrant or permit the use of expert testimony, two conditions must be met; first, the subject matter must be closely related to a particular profession, business or science and not within the common knowledge of the average layman; second, the witness must have such skill, experience or knowledge in that particular field as to make it appear that his opinion would rest on substantial foundation and would tend to aid the trier of fact in his search for truth.

Bridger v. Union Railway Co., 355 F.2d 382, 387 (6th Cir. 1966); see *Bratt v. Western Airlines*, 155 F.2d 850 (10th Cir. 1946). There is little doubt that in this case scientific (medical) evidence was needed to resolve a number of critical disputes. Furthermore, few would contend that these medical disputes were within the knowledge of the average layman absent expert testimony. Thus the evidentiary issue presented to the district court concerned Dr. Cibis' qualifications as an expert to give testimony as to whether Graham suffered

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14. An illustration by analogy points out the district court's error. If Dick sues Dentist Jane for dental malpractice, and Jane's defense is that her dental technique could not have caused the injury, expert dental testimony would be needed to determine if in fact, Jane's technique could have caused the injury. Furthermore, in such a context it would be an abuse of discretion for the court to not limit those who can testify on this issue to "experts" qualified to issue an opinion on dental technique.

If Jane's defense, however, was that Dick had suffered the injury of which he complains when he was struck in the mouth during a fight, the experts who could testify as to correctness of that possibility need not have the same qualifications as those needed for Jane's "technique" defense – in fact it would be an abuse of discretion to require the same standard.

a stroke prior to her receiving DTP vaccine.[15]

Dr. Cibis was a pediatric ophthalmologist who had received training in neurology as it relates to the eye. He was additionally one of Graham's original treating physicians. Dr. Cibis, upon the recommendation of Dr. Hertenstein, Graham's pediatrician, examined Graham on February 27, 1980 (when Graham was 11 weeks old and three weeks before her DTP vaccine) for an eye problem which he diagnosed as Cogan Apraxia (congenital motor apraxia). (Tr.1153-54).

The district court's approach to the admissibility of expert witness' testimony in this case was evidently fashioned by what it believed to be the central issue in the case: could endotoxins cause this type of damage? It ruled that no expert could testify who was not familiar with toxins. The district court stated the rule as follows:

> I don't know how anyone can fairly assess the significance of the time of that stroke in this case without addressing an awareness of the endotoxin, rule it in or rule it out.

(Tr. 2925).

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15. The Federal Rules of Evidence as they concern expert testimony are found in Rules 702 and 703 respectively. They read:

Rule 702. Testimony by Experts

If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise.

Rule 703. Bases of Opinion Testimony by Experts

The Facts or data in the particular case upon which an expert bases an opinion or inference may be those perceived by or made known to the expert at or before the hearing. If of a type reasonably relied upon by experts in the particular field in forming opinions or inferences upon the subject, the facts or data need not be admissible in evidence.

> The minute the [expert] says: "I have no wherewithall in the field of neurology, I have no appreciation of endotoxin or their significance or effects, if any" the witness isn't going to testify.

(Tr. 4585).

This approach forced Wyeth to limit the experts it called, to those who testified to *alternative theories* of injury to Graham. Thus, the district court compelled Wyeth to forgo critical testimony of a treating physician that Graham had suffered a stroke *prior* to her vaccination—testimony that if believed by the jury would have resulted in a verdict that Wyeth was not liable. It deprived Wyeth of a primary defense that it was not liable, due to an intervening cause *(i.e.*, that a pre-vaccination stroke caused Graham's injury) and instead left Wyeth with only an alternative theory that the DTP vaccine *could not*, rather than *did not*, cause a stroke.

While under the Federal Rules of Evidence a district court has substantial discretion in deciding which experts can and cannot testify, the district court may not employ that discretion to restrict viable and relevant theories offered by a party. In this instance the district court, by excluding Dr. Cibis' testimony, deprived Wyeth of crucial testimony, which if available to the jury, may well have swayed the jury in its determination. We cannot regard the exclusion of such evidence as harmless because it affected the substantial rights[16] of

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16. Fed.R.Civ. Proc. Rule 61 states:

Rule 61. Harmless error

> No error in either the admission or the exclusion of evidence . . . is ground for granting a new trial . . . unless refusal to take such action appears to the court inconsistent with substantial justice. The court at every stage of the proceeding must disregard any error or defect in the proceeding which does not affect the substantial rights of the parties.

See,e.g., Lusby v. T.G. & Y. Stores, Inc., 796 F.2d 1307 (10th Cir. 1986) (harmless error doctrine); *Prebble v. Brodrick*, 535 F.2d 605 (10th Cir. 1976) (same).

the defendant Wyeth, particularly when other expert testimony bearing on the same defense was also excluded.

B.

Dr. Breckbill, another physician called by Wyeth, was a specialist in pediatric radiology. Dr. Breckbill's credentials as a pediatric radiologist were detailed during his examination, and are extensive. On May 12, 1987, Graham underwent a CT head scan under the direction of Dr. Breckbill. He determined that she suffered a stroke. A large part of his testimony at trial dealt with the manner in which head scans are conducted. He testified that it was not uncommon for family practitioners or pediatricians to fail to diagnose brain lesions in infants, because of their young age, and the difficulty that physicians have in distinguishing normal from abnormal gross reflexes in infants. (Tr.3573-74).

During his testimony he acknowledged that he knew Graham had received a DTP vaccine on March 17, 1980 (Tr. 3580). After having reviewed the medical records and after acquainting himself with the testimony of other experts who testified as to the cause of Graham's disability, Dr. Breckbill stated:

> My opinion would be that the child had suffered a stroke when seen by Dr. Hertenstein, [she] had the stroke previous to the time that child was seen by him.

(Tr. 3895). We note parenthetically that Dr. Hertenstein examined Graham on February 2, 1980, more than six weeks before her DTP vaccination.

Dr. Breckbill explained the basis for his opinion that the stroke occurred sometime before February 2, 1980 by referring to the CT scan and the changes in both Graham's skull and brain. No objection was raised either as to Breckbill's qualifications or to his testimony at that

time. An extensive cross-examination occurred. On redirect examination, Wyeth inquired as to whether it was still Dr. Breckbill's opinion that Graham's stroke occurred before February 20, 1980 (the date of Dr. Cibis's examination). That question elicited an objection from Graham's counsel:

> The following colloquy took place:
>
> MR. WARSHAFSKY [Graham's attorney]: I object on the grounds that with the totality of the examination and now with what the Doctor had to examine and his background, I don't think the Doctor is qualified to give the opinion.
>
> THE COURT: Sustained.
>
> MR. WARSHAFSKY: And I move that his opinions given during direct testimony on the same subject be stricken.
>
> MR. HERRINGTON: [Wyeth's attorney]: Your Honor, there was no objection made during the direct examination.

(Tr. 3693).

* * * *

> MR. HERRINGTON: I'm not sure I'm clear. What is the Court ruling with regard to moving to strike his opinion with regard, on direct testimony that he gave?
>
> THE COURT: Sustained.
>
> MR. HERRINGTON: Where no objection was raised at the time.
>
> THE COURT: Well, you've reraised it and you restated it. Now its raised, and now I rule on it.
>
> MR. HERRINGTON: I'd like to make a proffer, your Honor, outside the hearing of the jury.

(Tr. 3697) Wyeth's counsel proffered the testimony of Dr. Breckbill as follows:

> MR. HERRINGTON: Based upon the information in the medical records that I asked you to review and that you have reviewed and the portions of Dr. Hertenstein's deposition that you were furnished and your reliance upon the head charts and their significance . . . do you still hold the same opinion you expressed yesterday that the stroke of Michelle Graham occurred before February 20, 1980 when the right fixed gaze was found by Dr. Hertenstein[17] [sic]? Do you still have the same opinion?
>
> DR. BRECKBILL: Yes.

(Tr. 3719). Thus, the testimony of Dr. Breckbill, which focused on events occurring *before* the DTP vaccination of Graham, was removed from the jury's consideration.

We do not focus on the fact that no objection was initially raised by Graham because we are satisfied that Dr. Breckbill's testimony should not have been stricken. His testimony not only bolstered Dr. Cibis' testimony but was directed to the very essence of Wyeth's defense, and was both highly relevant and material to that defense.

C.

In line with its earlier approach that no expert's testimony could be considered unless the doctor or expert had an appreciation of endotoxins or its effect, the district court also sustained Graham's objection to the testimony of Dr. Deitch.

Wyeth made an offer of proof outside the presence of the jury as to Dr. Deitch's testimony. Dr. Deitch, a Board

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17. Although the substance of Dr. Breckbill's testimony is unchanged, in fact it was Dr. Hertenstein who examined Graham on February 2, 1980 and Dr. Cibis who examined her on February 20, 1980.

certified pediatrician, reviewed Graham's medical history and had noted the fixed right gaze which had earlier been observed by Drs. Hertenstein and Cibis. The significance of this was, in Dr. Deitch's view, that "one of the things to be ruled out at that time [of Dr. Hertenstein's examination] was a stroke sometime prior to that [the time of Graham's DTP vaccination]." (Tr. 4353).

Dr. Deitch would also have testified that even a thorough pediatric examination of a child between two and three months of age [Graham was 7 weeks old at the time of Dr. Hertenstrein's examination and 11 weeks old at the time of Dr. Cibis'] would not necessarily reveal a stroke that had occurred because a loss of functions, slurring of speech, and distortions of the face, which manifest themselves when adults have strokes, do not show up in children at that young age.

The relevant and particular question that was excluded from jury consideration was: "Would the result of that stroke be apparent to a competent pediatrician performing such an examination at that time?" (Tr. 4161). Dr. Deitch's answer to that question would have been: "No." Thus, the affect of the district court's ruling was to prevent the jury's consideration of Dr. Deitch's confirmation that Dr. Hertenstein might not have initially recognized the manifestations of a stroke even though Graham might have suffered a stroke at a time prior to her vaccination.

D.

In sum, the result of the district court's rulings which prevented any evidence of a pre-vaccination stroke from reaching the jury, effectively vitiated a relevant theory which Wyeth was entitled to establish. As we have noted above, Wyeth's experts would have testified that Graham was originally diagnosed by her treating physician (Dr. Hertenstein) as having an eye

problem which he, as a pediatrician, could not diagnose. Dr. Hertenstein referred Graham to Dr. Cibis, a pediatric ophthalmologist, who examined Graham three weeks before her DTP vaccination. At that time, Dr. Cibis identified Graham's eye problem as relatively minor. Approximately one month later, Graham was vaccinated by Wyeth's DTP vaccine, and after that event, she was diagnosed as suffering from brain damage, which was caused by a stroke.

Graham thereafter had a CT scan taken by Dr. Breckbill. When the results of this CT scan were disclosed to Dr. Cibis, he indicated that, given what he now perceived from the CT scan, he would now have diagnosed Graham as having suffered a stroke prior to his original examination.

Supporting Dr. Cibis' diagnoses was Dr. Breckbill, a pediatric radiologist and a pediatric neuro-radiologist, who was prepared to testify that Graham had suffered a stroke before she had been vaccinated. Dr. Deitch, a Board certified pediatrician, was prepared to testify that it would not be uncommon for a pediatrician to fail to recognize signs of a stroke in an infant, thus giving additional credence to Wyeth's theory of pre-vaccination injury.[18]

While we obviously cannot, and do not, find that Graham's DTP vaccination occurred *after* she had suffered a stroke (fact finding here was a function for the jury), it is clear that causation evidence of this import could not be withheld from jury consideration. Thus, whether the district court's rulings excluding Dr. Cibis' testimony is considered alone, or is considered in conjunction with the exclusion of the testimony of Drs. Breckbill, and Deitch, we are satisfied that the district

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18. We do not elaborate on the district court's ruling restricting Dr. Pollack's examination, as Dr. Pollack's testimony was not focused specifically on the issue of pre-vaccination injury. In light of our disposition of this appeal, we express no opinion on the admissibility of Dr. Pollack's testimony.

court prevented the jury from hearing the opinion of these experts on the cause of Graham's injury. Moreover, as we have earlier observed, an error of this magnitude inevitably had to prejudice Wyeth's defense, and cannot be deemed harmless.

IV.

Wyeth also argues that the district court abused its discretion when it admitted an American Medical Association Ad Hoc Panel Report, "Pertussis Vaccine Injury," 245 JAMA 21:3083 (December 6, 1985) (PX376) into evidence, when it redacted the Report, and when it, contrary to the provision of Fed. R. Evid. 803(18), not only permitted the report to be read to the jury in its redacted form but then permitted the jury to receive the document as an exhibit. Wyeth charges that this document was so fatal to Wyeth's case that Wyeth was obliged to move for a mistrial.[19]

The Report's first sentence stated its objective:

> In an effort to ensure an adequate and uninterrupted supply of vaccine for mandated pediatric immunization and to encourage the continued timely administration of these vaccines, the American Medical Association formed a commission to explore the need for a compensation system for vaccine-injured patients.

The remainder of that paragraph and a portion of the succeeding paragraph addressed itself to the issue of establishing a federal vaccine compensation program as an exclusive remedy for any individual injured by a mandated vaccine and noted that there was only one remaining supplier of DTP — a supplier who might be unable to obtain insurance renewal.

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19. The district court characterized the AMA Report as "the smoking gun we have been looking for . . ." (Tr. 1627) and denied Wyeth's motion.

Other portions of the exhibit, while acknowledging that the Report did not have as its purpose stringent proof of causation of injury by the vaccine, did refer to injuries "reputed" to be vaccine-related and reported by television and radio news programs, newspapers or parents groups but whose relationship to DTP vaccine was not necessarily supported by medical evidence. It went on to state that it was the impression of the AMA panel that about 10% of patients exhibiting seizures may have residual brain damage after one year. Other probabilities of related injuries were discussed in the Report, although the panel noted that there was "no evidence that killed vaccine (such as [Wyeth's] pertussis vaccine) can cause any prolonged insidious or delayed deleterious effects (in contrast to live attenuated organism vaccine)." While the Report did not address the issue of whether DTP could cause retardation — but rather addressed itself to a proposed legislative solution to compensate vaccine victims — some of its content could be read as relating to the issues in this case. We reproduce in full in the margin, the one and one-half paragraphs of text redacted by the district court.[20]

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20. The redacted material read as follows:

In an effort to ensure an adequate and uninterrupted supply of vaccine for mandated pediatric immunization and to encourage the continued timely administration of these vaccines, the American Medical Association formed a commission to explore the need for a compensation system for vaccine-injured patients. From these deliberations recommendations for federal legislation were made and approved by the Association's House of Delegates in June 1984. Draft federal legislation was prepared calling for the establishment of a federal vaccine compensation program as an exclusive remedy for those seriously injured by mandated vaccines. There was considerable urgency since the number of national suppliers for one of these vaccines (diphtheria-tetanus-pertussis, or DTP) decreased from three to one. There also was a reasonable possibility that the sole remaining supplier would be unable to obtain insurance renewal.

The concern with DTP vaccine resides with its pertussis

Wyeth objected to the admission of the Report in its entirety, claiming that the Report was neither a scientific nor a clinical study nor a learned treatise. It also objected to the court's *sua sponte* redaction of the introductory portion of the Report which, as noted, dealt with a proposed compensatory and insurance scheme. In addition, Wyeth contended that when the district court permitted the jury to have the redacted document in its possession during deliberations as a written exhibit, the district court had acted contrary to the express provision of Fed. R. Evid. 803(18) which provides that if a learned treatise is admitted "the statements may be read into evidence but may not be received as exhibits."

A.

Wyeth claimed among other things that the Report did not qualify as a learned treatise because Graham's expert had not established that it was a reliable authority within the meaning of Fed. R. Evid. 803(18).[21] Wyeth

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cell components, which occasionally induce severe neurological injury. In order to prepare an appropriate information base on potential pertussis vaccine injuries in the context of Congressional consideration of vaccine injury compensation legislation, . . .

American Medical Association Ad Hoc Panel Report, "Pertussis Vaccine Injury," 254 JAMA 3083 (December 6, 1985).

21. Fed. Rule of Evid. 803(18) reads:

The following are not excluded by the hearsay rule, even though the declarant is available as a witness:

* * *

(18) Learned treatises. To the extent called to the attention of an expert witness upon cross-examination or relied upon by the expert witness in direct examination, statements contained in published treatises, periodicals, or pamphlets on a subject of history, medicine, or other science or art, established as a reliable authority by the testimony or admission of the witness or by other expert testimony or by judicial notice. If admitted, the statements may be read into evidence but may not be received as exhibits.

also claimed that in order to be admitted into evidence, the Report would have to be demonstrated to be relevant to the facts of the case at issue.

Dr. Gilmartin, who testified on behalf of Graham, testified only that the panel was a prestigious panel, and that the Journal of the American Medical Association, in which the Report appeared, was an authoritative publication. Significantly, Dr. Gilmartin did not testify that the Report itself was a reliable authority or that it constituted a learned treatise. Moreover, because the Report did not deal with the causal relationship between DTP and stroke, Wyeth asserted that a specific issue in this case which focused on causation was not addressed and therefore the Report was irrelevant.

Our reading of the record does not disclose Wyeth's specific objection to the introduction of this Report on the ground that the foundation for its introduction was inadequate. Rather, Wyeth objected strenuously to the Report on the grounds that its purpose was not to establish causation, but was rather tangential in the sense that it advocated a legislative compensatory scheme. Indeed, Wyeth's strongest objection was to the *sua sponte* redaction of a portion of the Report which deprived the jury of knowledge that the Report did no more than propose a plan to compensate any DTP victims. In the absence of a specific objection to the manner in which Graham laid the foundation for the Report's introduction, we cannot say that the district court judge would have abused his discretion had he permitted the entire Report in evidence, leaving it to Wyeth to cross-examine Dr. Gilmartin on the purpose of the Report. By doing so, Wyeth could have clarified the relevance and import of the Report itself.

B.

Whether or not the full Report was admissible in evidence within the ambit of Fed. R. Evid. 803(18), the

district court's subsequent action in *sua sponte* redacting a significant portion of the Report stands on a different footing. After Wyeth had objected to the relevancy of the Report because the panel had not established a causal relationship between DTP vaccine and encephalopathy, the district court on its own motion redacted the first paragraph and a substantial portion of the second paragraph of the Report. The sentences redacted, as we have noted earlier, contained a statement as to the purpose of the Report (compensation) and a reference to the possibility that insurance might be unavailable. The district court recognized that the issue of compensation as presented in the Report was irrelevant to the issues of this case, but by redacting all reference to compensation the court unwittingly distorted the thrust of the Report. Not only was the purpose and theme of the article withdrawn from the jury's consideration, but the district court explicitly ordered that Wyeth could not cross-examine any witness on the material which appeared in the redacted paragraphs.

The district court answered Wyeth's observation that the subject of the Report's purpose would have to be addressed in cross-examination, by stating:

> THE COURT: Let me see if I can make it clear then. You're entitled to get into it [the Report], but you're admonished not to get into anything mentioned in the first paragraph.[22] (Tr. 1629).

* * *

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22. We cannot reconcile the district court's order redacting only the first paragraph with the actual redaction of the exhibit which included an additional portion of the second paragraph. No explanation appears as to why more than the first paragraph was redacted. Inasmuch as we hold that the district court improperly redacted any part of the report once it had decided to admit the entire report into evidence, the additional redaction only added to the error.

> THE COURT: You can take out the first paragraph which gives rise to the reason it [the Report] was formulated, ostensibly, because they were about the formation of some kind of compensation program. After the first paragraph, there isn't a thing in this paper you can't go into. (Tr. 1667).
>
> * * *
>
> THE COURT: Very well. I only say, seem [sic] to me we could cut out the first paragraph. I've already told the jury the first paragraph's irrelevant. It's no longer of concern to them. Take it out. All of you can use the exhibit. . . . (Tr. 1667).

Through its redaction, the district court admitted evidence into the case which could only mislead the jury. By prohibiting cross-examination about the true purpose of the Report the district court compounded its error. Moreover, although Dr. Gilmartin testified to some statements in the redacted Report having to do with the panel's recitation of probability of vaccine causation, (Tr. 1631) the entire redacted Report was given to the jury for their study during deliberations. What the last provision in Fed. R. Evid. 803(18) seeks to preclude by prohibiting the receipt of the written exhibit into evidence is described in Weinstein's Evidence as:

> To insure that the jurors will not be unduly impressed by the treatise, and that they will not use the text as a starting point for conclusions untested by expert testimony, the last paragraph of Rule 803(18) bars the admission of treatises as exhibits so that they cannot be taken into the juryroom.

J. Weinstein & M. Berger, 4 Weinstein's Evidence ¶803(18)[02].

Thus, as Wyeth contends in its brief on appeal — a contention with which we agree:

> The redacted portion of the report was critical. It explained the background and limited purpose of the report, namely to provide an information base on *potential* pertussis vaccine injuries for Congressional consideration of vaccine injury compensation legislation.
>
> The redaction of such material made the redacted report prejudicially [sic] misleading. By excluding such information, PX376 was made to look like an AMA report on causation, when it was not. In fact, the reported stated that "[w]ithin the purpose of this report," which purpose was redacted, "stringent proof of causation by the vaccine was not required." Nonetheless, the trial court described the report as a "smoking gun" on the issue of causation, and, indeed, in its redacted form it was a deadly weapon. The judge then admonished the parties not to mention anything contained in the redacted portion of PX376.
>
> Wyeth was severely prejudiced because of its inability to counter the portions of PX376 read into evidence by Dr. Gilmartin (plaintiff's medical expert) over Wyeth's objection, which appeared to establish that the AMA had concluded that DTP causes encephalopathy, when there is no scientific evidence establishing such causation.

(Wyeth br. at 88-1339, p. 51) (Internal citations omitted).

We are satisfied that the district court abused its discretion in redacting the portions of the Report which explained the Report's purpose and background and in prohibiting Wyeth from addressing those issues on cross-examination or through its own witnesses. We are also satisfied that it was improper to submit the Report in its redacted version to the jury in contravention of Fed. R. Evid. 803(18). We need not decide if this abuse

of discretion on the part of the district court, even though it may have been well intentioned, would by itself require a reversal of the judgment in favor of Graham. We are convinced however, that when we consider both the exclusion of the testimony of Wyeth's experts (Drs. Cibis, Breckbill, and Deitch) which the district court ordered, together with the unfortunate redaction of the Report and its submission to the jury as an exhibit, the judgment in favor of Graham cannot stand.

V.

Wyeth has also asserted additional alleged errors which do not require extensive discussion in light of our disposition of this appeal. All of the other errors asserted are matters which were peculiar to the trial whose judgment we are reversing, and hence may not occur, or may not be the subject of error, at the new trial which we have directed the district court to hold. Indeed, Wyeth's appeal from the district court's denial of its Fed. R. Civ. Pr. 60(b) motions fall within the same category. In normal course we would not discuss in this appeal the denial of Wyeth's post-trial motions, as it is apparent that at the retrial the very information which Wyeth claims to have newly discovered will, if it desires, become part of its defense.

Nevertheless, because the evidence which was the subject of Wyeth's 60(b) motions goes to the heart of the testimony of Graham's experts and would in our opinion require a new trial, even had we not decided that the evidentiary errors on direct appeal required reversal, we will explain our conclusion that a new trial was required on the grounds of newly discovered evidence.

A.

A final error was committed by the district court in its denials of post-trial relief to Wyeth under F.R.Civ.P.

60(b) when Wyeth sought a new trial on the grounds of newly discovered evidence. The grant of denial of a Rule 60(b) motion is reviewed for abuse of discretion; *In re International Coating Applicators*, 647 F.2d 121, 124 (10th Cir. 1981).[23]

B.

At the conclusion of trial the jury awarded Graham $15,000,000 in compensatory damages. Through later depositions taken in other DTP cases unrelated to the instant proceeding, Wyeth discovered that two of the key

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23. It is unclear if jurisdictionally a district court can ever grant a rule 60(b) motion after a notice of appeal has been filed. The procedure approved by us in this case is for the district court to indicate that it would grant the 60(b) motion if it had jurisdiction, and for the our court to then remand the case to the district court for that court to decide the motion; see *Blinder, Robinson & Co. v. SEC.*, 748 F.2d 1415, 1420 (10th Cir. 1984) ("In ordinary civil cases the rule is that after an appeal has been taken the district court retains jurisdiction to consider and deny a rule 60(b) motion and, if it indicates that it will grant the motion, the movant may then ask the court of appeals to remand the case so that the district court may act.") quoting *Aune v. Reynders*, 344 F.2d 835, 841 (10th Cir. 1965); see also *United States v. 397.51 Acres of Land*, 692 F.2d 688, (10th Cir., 1982).

As we reconstruct the sequence of events from the docket sheets, the jury verdict in favor of Graham was entered on October 15, 1987. Timely motions were made by Wyeth for judgment NOV or for a new trial. These were denied on February 2, 1988 followed by a timely notice of appeal, the time for which had been tolled by Wyeth's post trial motions. Thereafter, on April 15, 1988, Wyeth moved for relief from the Graham judgment pursuant to Fed. R. Civ. Pro. 60(b). On July 19, 1988, the district court denied Wyeth's 60(b) motion which was followed by Wyeth's motion for reconsideration — a motion that was also denied by the district court. Wyeth then appealed on April 17, 1988 from the denial of its original 60(b) motion.

On October 13, 1988, Wyeth moved again for relief of judgment under Fed. R. Civ. Pro. 60(b). That motion was also denied on February 16, 1989. A timely appeal was taken from that denial as well.

expert witnesses who had testified on Graham's behalf, had erred in their testimony as to the toxicity of Wyeth's vaccine. These two witnesses, Dr. Geier and Dr. Zahalsky, both misstated[24] in their testimony to the *Graham* jury, the results of Dr. Geier's experimentation respecting the levels of endotoxin in Wyeth's DTP vaccine. This evidence was addressed to Wyeth's alternative defense: that DTP vaccine could not have caused Graham's stroke. Both of Wyeth's 60(b) motions concerned this testimony.

At trial, in the present case, Dr. Geier had testified extensively as to the critical relationship between the toxicity of any pertussis vaccine and the level of endotoxin. The thrust of his testimony was that the higher the level of endotoxin, the greater the danger that any given vaccination would lead to adverse reactions, including those allegedly suffered by Graham. Dr. Geier stated that the "[m]ore the endotoxin, the more severe [the] reaction" (Tr. 892). Specifically, Dr. Geier stated that the endotoxin content of Wyeth's vaccination was 240 micrograms per milliliter (Tr. 1028) — a level four times higher than that of the next most toxic pertussis vaccine made by other pharmaceutical companies and 2400 times higher than the least toxic of the other pertussis vaccines. (Tr. 1028-31).

In fact, it later appears that Dr. Geier had erred in his computation of the toxicity of the Wyeth's DTP vaccine. Instead of Wyeth's vaccine having an endotoxin level of 240 micrograms per milliliter, it actually had only a level of 20 micrograms per milliliter. Thus, when Dr. Geier was deposed in a later case entitled *Talley v. Wyeth Laboratories*, (case no. 87-349-C, E. D. Okla., Feb. 24, 1988), he testified:

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24. We assume that any error that occurred in Drs. Geier's and Zahalsky's testimony was due to unintentional mathematical calculations.

> Q: Your initial estimate of this Lederle [DTP vaccine] made by Wyeth was that it had 240 micrograms per milliliter, and then on subsequent reflection and further testing, you found that it had tenfold less than that; is that correct?
>
> A: That's right, that one looks like an error of — what we call an order of magnitude error, that is when I did the calculation, I must have missed a zero
>
> Q: And a tenfold difference can be pretty significant in terms of your opinion, can't it?
>
> A: Sure.

(Tr. 468).

Dr. Geier, in a number of other depositions, had given substantially identical testimony to the effect that Wyeth's vaccine is not as toxic as he originally thought it was.[25] This testimony substantially undermined the weight of the evidence to which he testified in Graham's case.

Almost by definition, any error in Dr. Geier's testimony had to affect the testimony and conclusions of Dr. Zahalsky, who when he testified, relied on Dr. Geier's calculations. Thus Dr. Zahalsky testified at trial that: And the reason I chose to identify this [a high endotoxin value] as probably the more likely value, the higher value, is because I had discussed with Dr. Geier what his analysis revealed. . . . I chose to take this value here [the higher endotoxin number] because he [Dr. Geier] had actually assayed [Wyeth's vaccine] which had 240 micrograms per mil[liliter].

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25. In the cases of *McLean v. Wyeth*, 86-4077 (W.D. Ark. 1988), *Cavallo v. Wyeth*, Circuit Court, Milwaukee County, Milwaukee, Wis. 716-507, and *Cooper v. Wyeth*, 86-1177C (E.D. Miss. 1987), Dr. Geier acknowledged the error of his testimony in the *Graham* case. These depositions can be found in Wyeth's Addendum of Exhibits, Volume I, 89-3066.

(Tr. 639). Dr. Zahalsky also identified himself as a "collaborator" with Dr. Geier on those experiments (Tr. 498) and at the Graham trial, Dr. Zahalsky substantiated the validity of his results by identifying them with the results of Dr. Geier's experiments. Thus, any error in Dr. Geier's experiments had to affect the testimony of any other expert who relied on Dr. Geier's results.

C.

After discovering that Dr. Geier's testimony in Graham had an erroneous basis, Wyeth filed its F.R.Civ.Pro. 60(b) motions in the district court, seeking post-trial relief from Graham's judgment based upon these errors in the testimony.

Federal Rule of Civil Procedure 60(b) provides for relief from judgments or orders. Subsection (b) specifies that such relief may be available where among other things:

> (2) Newly discovered evidence which by due diligence could not have been discovered in time to move for a new trial under rule 59(b); or
>
> * * *
>
> (6) Any other reason justifying relief from the operation of the judgment.

The district court denied Wyeth's motions for post-judgment relief. We cannot agree with the district court's resolution of Wyeth's motions grounded on newly discovered evidence. Thus, we hold that the district court abused its discretion in refusing to grant Wyeth's rule 60(b) motions, to the extent that Wyeth predicated its motions on alleged newly discovered evidence.

D.

For newly discovered evidence to provide a basis for a new trial under Fed. R. Civ. Pro. 60 (b)(2), Wyeth was required to satisfy five conditions:

Wyeth had to demonstrate that:

(1) the evidence was newly discovered since the trial;

(2) Wyeth was diligent in discovering the new evidence;

(3) the newly discovered evidence could not be merely cumulative or impeaching;

(4) the newly discovered evidence had to be material; and

(5) that a new trial, with the newly discovered evidence would probably produce a different result.

See *Ag Pro. Inc. v. Sakraida,* 512 F.2d 141, 143 (5th Cir. 1975), *rev'd on other grounds,* 425 U.S. 273 (1976).

In its July 19, 1988 disposition of Wyeth's 60(b) motion, the district court concluded that Wyeth had not met three of the five requirements for relief under 60(b). The district court found that Wyeth had not exercised diligence in obtaining the new evidence; that the evidence did not meet the test of materiality and that even with this new evidence, a new trial would probably not produce a different result.

In so holding, the district court did not dispute that the evidence was newly discovered, i.e., that Dr. Geier's miscalculations did not come to light until after the Graham trial had concluded.[26] Nor did it find that this

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26. *See Rosebud Sioux Tribe v. A. & P. Steel, Inc.* 773 F.2d 509 (8th Cir.), *cert. denied,* 469 U.S. 1072 (1982) (a witness' perjury in his deposition and at trial, [like Dr. Geier's miscalculation of the

new evidence of Dr Geier's was cumulative or could be characterized as impeaching. We agree that these two prongs of the five-prong test have been satisfied. Indeed, as we discuss below, we are persuaded that all five requirements of 60(b) were met by Wyeth.

We reject Graham's and the district court's assertions that Wyeth's decision not to duplicate all of Dr. Geier's experiments was a form of "lack of diligence." Rule 60(b) does not set that high a standard. If such a standard was mandated, there would be few cases where a 60(b)(2) motion could be granted, inasmuch as the movant would have to demonstrate that it could not have independently confirmed the erroneous calculation of the results.[27] As Wyeth contends, "The change in Dr. Geier's endotoxin figure was produced by a change in the value of the Reference Standard used to calculate the endotoxin content of the Wyeth DTP vaccine (Geier Deposition in *Talley v. Wyeth,* L86-4077 W.D. Ark. 1988, pp. 458, 463). Since the change in the Reference Standard was not made until after Dr. Geier testified at trial, Wyeth could only have discovered the evidence after trial." (Wyeth br. at 88-2302, p. 15).

So too, we reject Graham's assertion (Appellee's br. at 88-2302, p. 20 n.4) that because Dr. Geier already knew about the potential mistakes in his research at the time of his testimony in Graham's trial, it was Wyeth's lack of "diligence" that caused Wyeth to fail to discover that fact by asking Dr. Geier if he was mistaken! We must assume that Dr. Geier was unaware of the errors in his testimony at the time he testified. Moreover, the miscalculations made by Dr. Geier changed the entire complexion of the case. Had the Graham jury been

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NOTES *(Continued)*

toxicity level of DTP] constituted newly discovered evidence.

27. The intent of the diligence requirement is to insure that litigants do not "hold back" evidence so as to be granted a new trial if the first trial is lost.

alerted to the correct calculations of toxicity, it may well have taken a different view of the case.

The third prong of the test (that the evidence must not be merely cumulative or impeaching) appears to us, (as it must have appeared to the district court) to have been satisfied because of the gravity of Dr. Geier's error in miscalculating the toxicity of Wyeth's vaccine. We cannot help but observe that this error was testified to by Graham's most significant expert—Dr. Geier—who testified in support of her claim.

The fourth prong of the test (that the evidence must be material) was satisfied because Dr. Geier's testimony focused on one of the most significant aspects of Graham's claim—the allegedly high endotoxin level of Wyeth's pertussis vaccine. Dr. Geier, as noted was Graham's key witness on this issue. Without evidence being adduced as to high endotoxin levels, the case might not have even reached the jury.[28] Additionally, a proper calculation of the endotoxin level by Graham's experts might have lead the district court, in either its summary judgment opinion or in its consideration of the motion to strike Wyeth's §402A comment (k) defense to "design defect" strict liability, to rule that Wyeth's vaccine was "unavoidably unsafe" and thus exempt from liability under §402A comment (k) from all but

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28. We are also persuaded that Dr. Zahalsky's testimony was gravely undercut by Dr. Geier's failure to analyze his data. Dr. Zahalsky himself has significantly recanted much of his testimony in Graham's case in other testimony given in other cases. Thus for example he seems to have lowered his estimate of the endotoxin level in Wyeth's vaccine from 353 micrograms per milliliter (Tr. 638-639), the amount he testified to in Graham's case to somewhere between 7.5 - 75 micrograms in other cases (*Overlay v. Warner Lambert* (IP83-1780-C) (S.D. Ind. 1986), and *Knudsen v. Connaught Laboratories* (85-703-CIV-J-16) (M.D. Fla. 1987). A twelve fold decrease in Dr. Geier's measurements would lead to a decrease in Dr. Zahalsky's measurements from 353 to 30 micrograms per milliliter. These depositions can be found in Wyeth's Addendum of Exhibits, I, 89-3066.

negligence claims. We hold that the district court's perception of this testimony as not being material was an improper exercise of the district court's discretion. Contrary to the district court's view, we cannot regard the evidence in question as less than material.

Finally we are left with the fifth prong of the Rule 60(b) calculus – whether the new evidence would have probably lead to a different result at trial. This prong of the test is logically the one that requires the most deference to the district court – that court which heard all of the evidence, which was present at trial to examine the demeanor and credibility of all of the witnesses, and which had its finger most closely on the pulse of the trial. As we stated in *Kodekey Electronics, Inc. v. Mechanex,* 486 F.2d 449, 458 (10th Cir. 1973):

> Such a determination [would the new evidence have lead to a new trial?] is not particularly favored by the courts, and rests largely and almost wholly within the sound judicial discretion of the trial court. Whether the newly discovered evidence would be likely to change the result of the district court's decision is one peculiarly within the determination of but one man – the trial judge.

However, we have observed that where the subject of a district court ruling involved experimental evidence which should not have been allowed and which misled the jury, this court has reversed the district court notwithstanding the general deference which is normally accorded to a trial judge on these matters. *See Jackson v. Fletcher,* 647 F.2d 1020, 1027 (10th Cir. 1981). We recognize that *Jackson* was decided on direct appeal and not on appeal from a post-trial 60(b) motion, as is the case here. Nevertheless and even though not directly on point in this appeal, we are enlightened by and subscribe to Judge Doyle's statement in *Jackson* that, "in many instances, *a slight change in the conditions under which the experiment is made will so distort*

the result as to wholly destroy its value as evidence, and make it harmful, rather than helpful." (Emphasis added.) (*quoting Navajo Freight Lines v. Mahaffy,* 174 F.2d 305, 310 (10th Cir. 1949).) This pracept is even more relevant in a case such as Graham's where the jury is less able to resolve technical and scientific facts by relying on its own common sense and experience.

The district court found no impropriety or unfairness in testimony of Drs. Geier and Zahalsky even when the deficiencies in their testimony were brought to his attention by Wyeth's 60(b) motions. We are hard pressed to understand that conclusion in light of the context in which their evidence was presented at trial. Elementary reasoning and our complete review of the trial record reveals that an accurate presentation of the endotoxin level in Wyeth's vaccine could not help but dilute the total impact of Graham's case. Moreover, Rule 60(b) is intended "to prevent the judgment from becoming a vehicle of injustice," *see United States v. Walus,* 616 F.2d 283, (7th Cir. 1980), and the Rule is to be construed liberally to do substantial justice.

It is true, we cannot say with certainty that at a new trial Graham may not again prevail, however with the significant modification in Dr. Geier's testimony which Wyeth has now discovered, it is probable that a different result in the verdict would occur. We are not required in this context to deal with "certainties" but only "probabilities." The test is whether the new evidence introduced would *probably* produce a new verdict. We are satisfied, after having examined in detail the argument of both Graham and Wyeth in light of the entire record, that in this case, that probability exists.

Having concluded that the five requirements for relief from a judgment on the grounds of newly discovered evidence were satisfied by Wyeth when it discovered Dr. Geier's miscalculations as to the toxicity of Wyeth's vaccine, we hold that the district court should have exercised its discretion by vacating the Graham

judgment and by granting Wyeth a new trial.[29] Because it did not do so, we will reverse the orders of the district court denying Wyeth's post-trial relief. In doing so, we recognize that this holding with respect to Wyeth's 60(b) claims, accords with our holding with respect to trial errors, in that the dispositions of both appeals require a new trial. We assume that the miscalculations now disclosed in Dr. Geier's testimony will be corrected or addressed at a new trial if the same issues are presented.

VI.

We have held that trial errors and the discovery of new evidence by Wyeth compel a new trial to be held. We will, therefore, reverse the judgment in favor of Graham and remand to the district court for proceedings consistent with the foregoing opinion.

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29. Having determined that Wyeth has satisfied the requirements of Rule 60(b)(2), we do not find it necessary to address Wyeth's claim for relief from judgment under Rule 60(b)(6).

APPENDIX B

Michelle GRAHAM, an Infant Under the Age of Eighteen, Who Sues by Her Parents, Guardians and Next Friends, Charles GRAHAM and Tammy Graham; and Charles Graham and Tammy Graham, Individually, Plaintiff,

v.

WYETH LABORATORIES, A DIVISION OF AMERICAN HOME PRODUCTS CORPORATION, a Pennsylvania Corporation, Defendant.

No. 85-1481-K.

United States District Court,
D. Kansas.

July 21, 1987.

Order Nunc Pro Tunc July 22, 1987.

Andrew Hutton, Michaud, Hutton & Michaud, Wichita, Kan., for plaintiff.

Albert J. Knopp, Baker & Hostetler, Cleveland, Ohio, Alvin D. Herrington, Wichita, Kan., Hedy M. Powell, Philadelphia, Pa., for defendant.

MEMORANDUM AND ORDER

PATRICK F. KELLY, District Judge.

This case is before the court on defendant's motion for summary judgment. Plaintiffs Charles and Tammy Graham claim their infant daughter, Michelle Graham, sustained severe and irreversible brain damage after being vaccinated against diptheria, pertussis (whooping cough) and tetanus. The DPT vaccine she received was manufactured and distributed by defendant Wyeth Laboratories ("Wyeth").

The plaintiffs, parents and daughter, brought this diversity action asserting claims of strict liability and

negligence for design defect and failure to warn, breach of the implied warranties of merchantability and fitness for a particular purpose, and intentional misrepresentation. Plaintiffs also seek punitive damages, claiming the defendant willfully, wantonly and recklessly failed to adequately warn of the possible severe reactions to the DPT vaccine and willfully failed to rectify the product's design.

Defendant has moved for summary judgment, contending that federal law preempts plaintiffs' claims in their entirety. Alternatively, defendant contends that under Kansas laws as set forth in *Johnson v. American Cyanamid,* 239 Kan. 279, 718 P.2d 1318 (1986), this court must find as a matter of law that DPT vaccine is an "unavoidably unsafe" prescription drug which contains an adequate warning, and enter judgment in defendant's behalf.

After considering all well-pleaded facts in plaintiffs' favor, the court is convinced that defendant is not entitled to summary judgment and this case must proceed to trial. As will be explained herein, the court finds Congress did not intend to preempt state tort claims asserted by a victim of an adverse reaction to an FDA-approved drug. Further, the court finds that *Johnson* is distinguishable from the case at bar and does not require the entry of judgment in defendant's behalf.

FACTS

Defendant Wyeth manufactures the DPT vaccine which is used to immunize children against the diseases of diptheria, pertussis (whooping cough) and tetanus (lockjaw). The vaccine is administered to infants at two, four, six and eighteen months. A booster is administered prior to the child's entrance into school.

The DPT vaccine is comprised of three component parts which will be more thoroughly described herein. Those components are diptheria toxoids, tetanus tox-

oids, and a pertussis whole cell vaccine. It is the pertussis component which causes severe reactions such as suffered by Michelle Graham.

While plaintiffs contend the pertussis component of the vaccine could have been safer, they do not argue that a pertussis vaccine is unnecessary or that it has not saved millions of lives. In the early 1900s, pertussis was a leading cause of death in children in this country.

> In 1934, when this country suffered its worst pertussis epidemic, there were 265,000 reported cases of pertussis per year, and 7500 related deaths. Hinman and Koplan, *Pertussis and Pertussis Vaccine: Re Analysis of Benefits, Risks and Costs,* Journal of the American Medical Association (June 15, 1984). By the early 1940s, pertussis was responsible for two and one-half times the number of deaths as all of the following diseases combined: measles, mumps, rubella, diptheria, polio, meningitis, chicken pox, and scarlet fever. *Id.*

Hurley v. Lederle Lab., Div. of American Cyanamid, 651 F.Supp. 993, 995 (E.D.Tex. 1986). The DPT vaccine containing the "whole cell" pertussis vaccine was licensed by the FDA in 1949. Due to the widespread use of the vaccine in this country, pertussis has virtually been eradicated. However, because of the persistent nature of the pertussis bacteria, there is a continuing and substantial risk of epidemics if the use of the vaccine were to decline significantly. *Hurley,* 651 F.Supp. at 995.

The nature of the DPT vaccine and its component parts was recently capsuled by the Ninth Circuit, and is instructive herein:

> By introducing an antigenic factor into the body, vaccines stimulate the production of antibodies that protect against disease. Some infectious organisms, such as those causing diptheria and tetanus, excrete

> soluble toxins insoluble by medical research. The toxin is inactivated with formaldehyde and transformed into a toxoid. The toxoid is then used in a vaccine, as it can immunize against disease by stimulating the production of antibodies in the recipient, even though it has lost its own poisonous qualities.
>
> This is not the case, however, with [the Pertussis component]. The [Pertussis] vaccine is a so-called whole cell vaccine because it contains whole killed pertussis organisms. The whole organism is used because the pertussis organism contains fifteen or sixteen different antigens, and medical science has yet to isolate the one that stimulates protection against the disease. See *Tinnerholm v. Parke, Davis & Co.*, 411 F.2d 48, 50 (2d Cir. 1969).

Toner for Toner v. Lederle Laboratories, 779 F.2d 1429, 1430 (9th Cir. 1986). Because the whole cell vaccine retains its poisonous qualities, it is "neurotoxic" and can cause adverse reactions which may be mild (local), or severe. Mild reactions may include swelling, fever, irritability, and crying spells. Severe reactions include encephalopathy, paralysis and death. The expected rate of such reactions is controverted by the parties. Defendant claims about one out of every 7,000 children will suffer high fever or convulsions while one of every 100,000 children will suffer brain damage; plaintiffs claim these figures are inaccurate as to the Wyeth vaccine because they are based on faulty data. Plaintiffs further contend that Wyeth is aware that the incidence of severe reactions is actually much higher.

In recognition of the dangerous propensities of the whole cell vaccine, efforts have been made to develop a fractionated cell pertussis vaccine. During the 1950s, the Eli Lilly Company developed a "split cell" vaccine called Tri-Solgen. Early studies indicated this vaccine was less toxic than the whole cell and it was approved by

the FDA in 1967. At that time, Lilly occupied a substantial share of the DPT market. In 1975, Lilly withdrew from the vaccine business and sold its Tri-Solgen vaccine to Wyeth. According to plaintiffs, in an effort to save on cost, Wyeth substituted its own "ingredients" (or "strains") into the Lilly "recipe" for the split cell vaccine. Wyeth then attempted to license this vaccine, but no license was granted by the FDA. Wyeth has made no further attempts to license a fractionated cell vaccine. Moreover, no such vaccine is licensed in this country today.[1] Of course, a pharmaceutical company is prohibited from marketing a product absent a license—to do so would constitute a criminal offense.[2] 21 U.S.C. §§331(d), 333(a), 355(a); *see also Toner v. Lederle,* 779 F.2d at 1431; *but see* 21 CFR 620.1 (allowing for manufacture of "either killed *whole* Bordetella pertussis bacteria or a *fraction* of Bordetella pertussis bacteria." [emphasis added]).

On March 17, 1980, plaintiff Michelle Graham, who was only a few months old, was administered defendant's DPT vaccine by a nurse at a county office of the Missouri Department of Health. Shortly thereafter Michelle developed a severe and irreversible neurological condition known as encephalopathy. For the purposes of

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1. Japan has developed and is currently using a pertussis toxoid (i.e., acellular) vaccine. Japan's vaccine is purported to be as efficacious as the whole cell vaccine, but far less reactive. Lederle Laboratories is currently attempting to negotiate for, or duplicate, the Japanese vaccine. *See Toner,* 779 F.2d at 1431.

2. "[T]he fact that a fractionated cell vaccine is not now licensed does not mean it is disapproved—it merely means either that no manufacturer has sought and obtained approval or that, in the instance of the 1972 refusal [of Wyeth's split-cell vaccine] by a review panel of the Bureau of Biologics, the application therein failed to make an adequate showing of safety or efficacy which is not to say that another manufacturer could not have made a successful application." *Toner v. Lederle Laboratories,* 112 Idaho 328, 732 P.2d 297, 313 (1987) (Huntley, J., concurring).

this motion, the court will assume the plaintiff's condition was caused by the pertussis vaccine.

Wyeth furnished medical practitioners who purchased the vaccine with pamphlets describing contraindications and possible adverse reactions to the drug's use. The pamphlet in use at the time of Michelle Graham's immunization stated, in pertinent part:

> The below-listed serious, and occasionally fatal, adverse reactions *have been reported* following administration of pertussis-vaccine-containing preparations. The incidence of these reactions is unknown, but they seem to be exceedingly rate . . .;
>
> 1. Severe temperature elevations—105°F. or higher.
>
> 2. Collapse with rapid recovery.
>
> 3. Collapse followed by prolonged prostration and a shock-like state.
>
> 4. Screaming episodes characterized by a prolonged period of peculiar crying during which the infant cannot be comforted.
>
> 5. Isolated convulsion(s) with or without fever.
>
> 6. Frank encephalopathy with changes in the level of consciousness, focal neurological signs, and convulsions with or without permanent neurological and/or mental deficit.
>
> 7. Thrombocytopenic purpura.
>
> The occurrence of sudden-infant-death syndrome (SIDS) *has been reported* following administration of DTP. *The significance of these reports is unclear.* It should be kept in mind that the three primary immunizing doses of DTP are usually administered to infants between the age of 2 and 6 months and that approximately 85 percent of SIDS cases occur in the period 1 through 6 months of age. . . .

. . . .

> Occurrence of any of the following signs, symptoms, or conditions following administration is a contraindication to further use of this product and/or pertussis vaccine as the single antigen: fever over 103°F (39°C); convulsion(s) with or without accompanying fever; alterations of consciousness; focal neurological signs; screaming episodes (also call screaming fits); collapse; thrombocytopenic purpura.
>
> The presence of an evolving or changing neurologic disorder is a contraindication to use.

(Emphasis added.) The pamphlet also contained a section entitled "Precautions"; Wyeth's precautions did not advise the doctor to determine the child's personal or family history of central nervous system disease or convulsions. Nor was the doctor advised as to treating adverse reactions.

Prior to the administration of the vaccine to Michelle Graham, Mrs. Graham was given some materials to read about the vaccine and was asked to sign a consent form. The information was prepared by the Missouri Department of Health and discussed the possible "side effects" from the vaccine, stating: "Rarely, about once in every 100,000 shots, inflammation of the brain (encephalitis) or brain damage may occur. Death may occur, even more rarely." The form warned that some children should not take the vaccine without consulting a doctor, including "[t]hose who have had convulsions or other problems of the nervous system," and "[t]hose who have had serious reactions to DTP shots before." The form invited the parent to ask questions prior to signing.

Mrs. Graham did have questions about the possibility of side effects. The nurse told her that the figures were "just statistics" and that "[i]t didn't really happen." When Mrs. Graham asked the nurse what would happen if she decided against having Michelle immunized, she

was told that the state would have her immunized and would then place her in a foster home. Mrs. Graham agreed to the vaccine because she though she had no choice.

As a result of Michelle Graham's severe and permanent injuries, plaintiffs filed suit in this court seeking compensation from Wyeth Labs. The thrust of plaintiffs' claims against Wyeth is that Wyeth has the technical know-how to develop (or design) a safer, yet equally efficacious, fractionated cell pertussis vaccine, but has refused to do so due to the increased manufacturing costs. Plaintiffs further assert that Wyeth has the technical ability to quantify the endotoxin level of each "batch" of vaccine produced, but has failed to do so. In this regard, plaintiffs contend the degree of endotoxin varies from vial to vial and lot to lot. Plaintiffs assert that Wyeth knew the reported risk factors of the whole cell vaccine were inaccurate and that the incidence of adverse reactions was actually much greater. Plaintiffs assert defendant had a duty to accurately disclose to the medical practitioner the inherent hazards of DPT, the contraindication to administering the vaccine, the alternatives to the whole cell vaccine, the likely results of refusing the vaccine, the antidotes to and treatment for adverse reactions to the vaccine, and early warning signs of an adverse reaction. Plaintiffs further assert Wyeth should have warned the medical practitioner to take a family history of the patient prior to administering the vaccine. As previously stated, plaintiffs proceed on theories of strict liability and negligence for design defect and failure to warn, breach of implied warranties, and intentional misrepresentation.

In ruling on a motion for summary judgment, the trial court conducts a threshold inquiry of the need for trial and grants summary judgment where no genuine issue of material fact exists and the moving party is entitled to judgment as a matter of law. *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, ____, 106 S.Ct. 2505,

2511, 91 L.Ed.2d 202, 213 (1986). The court is to be concerned with the sufficiency of the evidence, not its weight. *Casper v. C.I.R.*, 805 F.2d 902, 904 (10th Cir. 1986). Essentially, the inquiry is "whether the evidence presents a sufficient disagreement to require submission to a jury or whether it is so one-sided that one party must prevail as a matter of law." *Anderson*, 477 U.S. at ____, 106 S.Ct. at 2512, 91 L.Ed.2d at 214. There is no genuine issue for trial unless there is sufficient evidence—significantly probative or more than merely colorable—favoring the nonmoving party for a jury to return a verdict for that party. 477 U.S. at ____, 106 S.Ct. at 2511, 91 L.Ed.2d at 212. Where there is bit one reasonable conclusion as to the verdict and reasonable minds would not differ as to the import of the evidence, summary judgment is appropriate. 477 U.S. at ____, 106 S.Ct. at 2511, 91 L.Ed.2d at 213.

The movant's burden under Fed.R.Civ.P. 56 is to make an initial showing of the absence of evidence to support the nonmoving party's case. *Windon Third Oil and Gas v. Federal Deposit Ins.*, 805 F.2d 342, 345 (10th Cir. 1986). To show an absence of material fact, the movant must specify those portions of "the pleadings, depositions, answers to interrogatories and admissions on file, together with affidavits if any." Fed.R.Civ.P. 56(c). "[C]onclusory assertions to aver the absence of evidence remain insufficient to meet this burden." *Windon*, 805 F.2d at 345 n. 7. The opposing party may not rest upon mere allegations or denials in the pleadings, but must set forth specific facts supported by the kinds of evidentiary pleadings listed in 56(c) which demonstrate a genuine issue remaining for trial. *Anderson*, 477 U.S. at ____, 106 S.Ct. at 2511, 81 L.Ed.2d at 213. The evidence of the nonmoving party is deemed true and all reasonable inferences are drawn in his favor. *Windon*, 805 F.2d at 346.

I. The Preemption Doctrine

The doctrine of federal preemption arises from the Supremacy Clause of the United States Constitution:

> The Constitution and the laws of the United States which shall be made in pursuance thereof . . . shall be the supreme law of the land; and the judges in every state shall be bound thereby, anything in the laws of any state to the contrary notwithstanding.

U.S. Const., Art. VI, cl. 2.

Federal law may preempt state law in any of three ways:

> First, in enacting the federal law, Congress may explicitly define the extent to which it intends to pre-empt state law. E.g., *Shaw v. Delta Air Lines, Inc.*, 463 U.S. 85, 95-96, 77 L.Ed.2d 490, 103 S.Ct. 2890 [2898-99] (1983). Second, even in the absence of express pre-emptive language, Congress may indicate an intent to occupy an entire field of regulation, in which case the States must leave all regulatory activity in that area to the Federal Government. E.g., *Fidelity Federal Savings & Loan Assn. v. De la Cuesta*, 458 U.S. 141, 153, 73 L.Ed.2d 664, 102 S.Ct. 3014 [3022] (1982); *Rice v. Santa Fe Elevator Corp.*, 331 U.S. 218, 230, 91 L.Ed. 1447, 67 S.Ct. 1146 [1152] (1947). Finally, if Congress has not displaced state regulation entirely, it may nonetheless pre-empt state law to the extent that the state law actually conflicts with federal law. Such a conflict actually arises when compliance with both state and federal law is impossible, *Florida Lime & Avocado Growers, Inc. v. Paul*, 373 U.S. 132, 142-143, 10 L.Ed.2d 248, 83 S.Ct. 1210 [1217] (1963), or when the state law "stands as an obstacle to the accomplishment and execution of the full purpose and objectives of Congress." *Hines v. Davidowitz*, 312 U.S. 52, 67, 85 L.Ed. 581, 61 S.Ct. 399 [404]

(1941). See also *Fidelity Federal Savings & Loan Assn.*, supra, [458 U.S.] at 153, 73 L.Ed.2d 669, 102 S.Ct. [at 1222] 3014.

Michigan Canners and Freezers Assoc. v. Agricultural Marketing and Bargaining Board, 467 U.S. 461, 469, 104 S.Ct. 2518, 2523, 81 L.Ed.2d 399 (1984).

[1-6] Congressional intent to occupy a field may be either express or implied. *Hurley,* 651 F.Supp. at 997. Congress may evidence its intent to occupy a field expressly by words in the statute itself, or in the statute's legislative history. *Silkwood v. Kerr-McGee,* 464 U.S. 238, 249-50, 104 S.Ct. 615, 621-22, 78 L.Ed.2d 443 (1984). In the absence of express preemption, there is a strong presumption that Congress did not intend to displace state law. *Maryland v. Louisiana,* 451 U.S. 725, 726, 101 S.Ct. 2114, 2118, 68 L.Ed. 2d. 576 (1981); *Palmer v. Liggett Group,* 633 F.Supp. at 1173; *see also Silkwood,* 464 U.S. at 251, 104 S.Ct. at 623. ("[The Legislature's] silence takes on added significance in light of Congress' failure to provide any federal remedy for persons injured. . . . It is difficult to believe that Congress would, without comment, remove all means of judicial recourse for those injured. . . .") However, certain factors may exist in narrow instances from which courts will infer that Congress intended to pre-empt state law in a particular field. For instance, the scheme of the regulation may be so pervasive that courts will infer a congressional intent to occupy the field. *Rice v. Santa Fe Elevator Corp.,* 331 U.S. 218, 230, 67 S.Ct. 1146, 1152, 91 L.Ed. 1447 (1947). Or, the nature of the subject matter may be one which demands exclusive federal regulation in order to achieve national uniformity and courts will assume the federal law precludes enforcement of state laws on the same subject. *Florida Lime & Avacado Growers, Inc. v. Paul,* 373 U.S. 132, 143-44, 83 S.Ct. 1210, 1217-18, 10 L.Ed.2d. 248 (1963). Or finally, courts may determine that enforcement of

state law in a particular case may stand as an obstacle to the accomplishment of the purposes and objectives of Congress. *Hines v. Davidowitz,* 312 U.S. 52, 67, 61 S.Ct. 399, 404, 85 L.Ed. 581 (1941). *See also Pattern v. Lederle Laboratories,* 655 F.Supp. 745, 747 (D.Utah 1987); *Hurley,* 651 F.Supp. at 997.

In this case, defendant does not contend there has been express preemption. Rather, defendant contends that congressional intent to occupy the field of safety regulation in drug design, testing, and labeling should be implied from the pervasive scheme of the regulations the Food and Drug Administration (FDA) has promulgated pursuant to the authority granted under the Public Health Services Act (PHSA), 42 U.S.C. § 215 *et seq.* and the Federal Food, Drug and Cosmetic Act (FDCA), 21 U.S.C. § 301 *et seq.* Defendant further argues that an award of damages pursuant to state common law is "regulatory" in effect, and so must be deemed preempted. *See San Diego Building Trades Council v. Garmon,* 359 U.S. 236, 247, 79 S.Ct. 773, 780, 3 L.Ed.2d. 775 (1959).[3] In effect, defendant argues that it

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3. The *Garmon* decision involved federal regulation which, unlike the FDA at the time of Michelle Graham's injury, provided its own avenue for redress. This fact has caused at least one court to reject *Garmon* as authority that state tort remedies are "regulations". See *Palmer v. Liggett Group, Inc.,* 633 F.Supp. 1171, 1175 (D.Mass. 1986) (relied on *Silkwood* for proposition that compensatory awards have indirect and not regulatory-effect on defendant's behavior; "a lawsuit as the instant designed to compensate a victim of defendant's allegedly wrongful behavior, cannot be deemed a regulation . . ."). *See also MacGillivray v. Lederle Laboratories,* ____ F.Supp. ____ , No. 85-0422-JB, slip op. (D.N. Mex. Feb. 5, 1987) (the state tort law at issue here is remedial and compensatory in nature; its purpose is not regulatory and does not directly conflict with any aspect of the federal regulatory scheme . . . Nor would a state law damage claim necessarily frustrate the federal objectives behind the federal laws at issue here. . . . A tort judgment against a drug manufacturer may in fact accelerate the development of better, safer products. . . . Imposing a burden on the sale in the form of potential liability for defective design is distinguishable from a

would be improper for a lay jury to decide issues delegated to the expertise of a federal agency, and that any recovery based on tort theories would be inconsistent with the experts' previous informed decisions.

This court recognizes that the FDA's regulations of prescription drugs is indeed far-reaching, if not pervasive. The DPT vaccine is a prescription biologic subject to the provisions of the FDCA and the PHSA and the regulations promulgated thereunder. The FDA regulations encompass the licensing, production, testing, distribution, labeling, review and approval of all drugs and biologicals. *See generally,* 21 C.F.R. §§ 211, 310 *et seq.,* 600 *et seq.* Each DPT manufacturer must be licensed, 21 C.F.R. § 601.1, and must submit detailed descriptions to the FDA which define the process used to manufacture the vaccine, 21 C.F.R. § 601.2. The FDA must then review and approve the manufacturing process. 21 C.F.R. § 601.25. The FDA also issues an "establishment license" by conducting inspections of the manufacturers' facilities and prescribing certain personnel qualifications. 21 C.F.R. §§ 600.20, 211, subpart B. Specific tests are required for each batch of vaccine, the results of which must be submitted to the FDA for review. 21 C.F.R. §§ 610.1, 610.2. Further, the pertussis element of DPT can be produced only in conformity with 21 C.F.R. §§ 620.1-620.7. As to the "label" or "package insert", the FDA requires that the following information must be provided for a pharmaceutical product: (1) the composition of the product; (2) the product's administration schedule; (3) when the product's usage is indicated and contraindicated; and (4) the product's potential adverse reactions which have been associated with the product's use. 21 C.F.R.

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state seeking to exert actual control over the mode of manufacture or distribution of a specific product."). This court need not reach the issue of whether tort remedies "regulate" however, as it finds no implied intent to preempt.

§§ 610.60-610.65. The language used is subject to FDA approval, 21 C.F.R. §§ 1, 201; 50 Fed.Reg. 51108 (1985), and, once approved, the language cannot be changed without FDA approval; C.F.R. § 601.12.[4] Further, most states including Kansas, require a child to be vaccinated with DPT prior to entering public school. *See* K.S.A. 72-5209.

[7,8] The Supreme Court has held that federal regulations have "no less preemptive effect than federal statutes." *Fidelity Federal Savings & Loan Assn. v. De la Cuesta,* 458 U.S. 141, 153, 102 S.Ct. 3014, 3022, 73 L.Ed.2d 664 (1982). Thus, if the administrator promulgates regulations intended to preempt state law, a court's inquiry is limited and should "not disturb the agency's accommodation *'unless it appears from the statute or its legislative history that the accommodation is not one the Congress would have sanctioned.'* " *Patten v. Lederle Laboratories,* 655 F.Supp. at 747 (quoting *United States v. Shimer,* 367 U.S. 374, 381-82, 81 S.Ct. 1554, 1559-60, 6 L.Ed.2d 908 (1961)) (emphasis added). It cannot be overemphasized that *only* Congress has the power to preempt state law. *Rice,* 331 U.S. at 230, 67 S.Ct. at 1152. "[T]he federal government does not always speak with one voice and it is the intent of Congress that determines the scope of the preempted field. In such situations, the pronouncements of Congress must control over contrary statements by administrators." *Patten,* 655 F.Supp. at 750.

In order to find congressional intent to preempt state tort remedies, this court would have to conclude that the

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4. The regulations as to labeling do not specify mandatory wording, but are limited to the subject matter required. In *Muzatko v. International Playtex, Inc.* ____F.Supp. ____, No. 85-C-1540 (E.D.Wis. May 14, 1987), the court stated "[b]ecause tampon manufacturers are permitted discretion with respect to drafting their warnings, the court does not believe that the contents of the warnings constitute a 'requirement' as that term was intended by Congress to be preempted." At ____.

federal regulations were promulgated with the intent to *exempt* drug manufacturers from tort liability. This court cannot find that such an intent is implicit in the regulatory scheme governing the manufacture and distribution of DPT. To the contrary, Congress has recently clarified its intent that regulations should *not* preempt state tort remedies for victims of vaccine-related injuries. Such intent was manifested in the "National Childhood Vaccine Injury Act", which will be more fully explained herein. Moreover, FDA regulations of prescription drugs are generally viewed as setting *minimum* standards, both as to design and warning. *See, e.g., Brochu v. Ortho Pharmaceutical Corp.,* 642 F.2d 652 (1st Cir. 1981); *Salmon v. Parke-Davis & Co.,* 520 F.2d 1359 (4th Cir. 1975); *Griffin v. United States,* 500 F.2d 1059 (3d Cir. 1974); *Mac Gillivray v. Lederle Laboratories,* 667 F.Supp. 743, 746 (D.N.Mex. 1987); *Toner v. Lederle Laboratories,* 112 Idaho 328, 732 P.2d 297, 311 n. 12 (1987) ("FDA certification represents only the FDA's opinion, albeit an informed one, of the safety and efficacy of the drug. Regrettably, drugs occasionally prove not so safe as the FDA first believed."); *Wooderson v. Ortho Pharmaceutical Corp.,* 235 Kan. 387, 681 P.2d 1038, *cert. denied,* 469 U.S. 965, 105 S.Ct. 365, 83 L.Ed.2d 301 (1984); *Feldman v. Lederle Laboratories,* 97 N.J. 429, 479 A.2d 374 (1984); *Barson v. E.R. Squibb & Sons, Inc.,* 682 P.2d 832, 836 (Utah 1984); *Ferrigno v. Eli Lilly & Co.,* 175 N.J.Super. 551, 420 A.2d 1305 (1980); *Bristol-Myers v. Gonzales,* 548 S.W.2d 416 (Tex.Civ. App.1976); *McEwen v. Ortho Pharmaceutical Corp.,* 270 Or. 375, 528 P.2d 522 (1974); *Stevens v. Parke-Davis & Co.,* 9 Cal.3d 51, 107 Cal.Rptr. 45, 53, 507 P.2d 653, 661 (1973).

[9, 10] FDA certification is evidence, but not conclusive evidence, of the drug manufacturer's reasonableness; the trier of fact may assign FDA approval the weight it deserves. *See O'Gilvie v. International Playtex, Inc.,* 821 F.2d 1438 (10th Cir. 1987) (in affirming a jury

instruction from this court that FDA standards regarding tampons' Toxic Shock Syndrome warnings are "minimal", the court stated, "[c]ompliance [with FDA standards] is not dispositive under Kansas law if the plaintiff shows that a reasonable manufacturer would have done more." Thus, before a court can conclude that federal regulations—which traditionally set minimum standards—have preempted the ability of states to protect their citizens through the judicial process, "courts should wait for a clear statement of congressional intent to work such an alteration." *Ferebee v. Chevron Chemical Co.,* 736 F.2d 1529, 1543 (D.C.Cir.), *cert. denied,* 469 U.S. 1062, 105 S.Ct. 545, 83 L.Ed.2d 432 (1984).

[11] As previously stated, Congress has recently clarified that by promulgating regulations regarding vaccines, state tort remedies *were not* intended to be preempted. On November 14, 1986, Congress enacted the National Childhood Vaccine Injury Act (NCVIA) which added a new title to the Public Health Service Act of November 14, 1986, Pub.L. No. 99-660, 100 Stat. 3743. The NCVIA establishes a program for vaccine research, requires—for the first time—the reporting to federal officials of injuries resulting from routine childhood vaccines, and sets up a program to compensate persons who sustain vaccine-related injuries or death. The NCVIA is intended to achieve optimal prevention of infectious diseases through immunization, while also achieving optimal prevention against adverse reactions to vaccine. Thus, the NCVIA is premised on Congress' recognition of the "potential hazards of . . . vaccines and . . . the serious—and sometimes deadly—consequences they can have. This is particularly true with regard to the pertussis vaccine which is most commonly administered as part of a series of immunizations known as DPT. . . ." H.Rep. No. 908, 99th Cong., 2d Sess., pt. 1 at 6 (1986), *reprinted in* 1986 U.S. Code Cong. & Admin. News 6287, 6344, 6347.

The legislative history clearly reveals that Congress began with the assumption that, in the absence of the NCVIA, state tort law has— and would continue—to apply:

> [F]or the relatively few who are injured by vaccines—through no fault of their own—the opportunities for redress and restitution are limited, time-consuming, expensive, and often unanswered. *Currently, vaccine-injured persons can seek recovery for their damages only through the civil tort system or through a settlement arrangement with the vaccine manufacturer.* Over time, neither approach has proven satisfactory. Lawsuits and settlement negotiations can take months and even years to complete. Transaction costs—including attorneys' fees and Court payments—are high. And in the end, no recovery may be available. Yet futures have been destroyed and mounting expenses must be met.
>
> This approach has also been ineffective for the manufacturers of childhood vaccines. *This has become especially true in more recent years as the number of lawsuits—particularly those concerning the DPT vaccine—has increased.*

Id. (emphasis added.) Thus, the House Committee acknowledged that damages may be recovered in a judicial setting notwithstanding the FDA's exclusive regulatory authority over drug design, testing and labeling. In fact, one of the main purposes of the NCVIA was to remedy the shortcomings of the traditional tort remedies.

Under the new act, vaccine injury victims are divided into three groups: (1) those injured by a vaccine administered more than eight years before the enactment; (2) those injured by a vaccine administered less than eight years before the enactment; and (3) those

injured by a vaccine administered after the Act's enactment. The first group is not eligible under the NCVIA, but the Act makes "no changes from current law in such persons' legal rights or remedies." *Id.*, U.S. Code Cong. & Admin. News at 6354. The second group is eligible for compensation, but may instead choose to pursue a civil tort action. *Id.*, 1986 U.S. Code Cong. & Admin. News at 6355. The third group must complete the Act's compensation proceeding and reject its judgment before pursuing a civil action; however, a civil action is not foreclosed. *See Patten v. Lederle*, 655 F.Supp. at 749.

The NCVIA further evinces a congressional intent that civil tort actions were—and are—permissible despite compliance with the FDA regulations. (The defendant herein has argued that tort remedies may be pursued against a drug manufacturer only when there is evidence that regulations were violated.) Under the new act, there is a presumption that the vaccine contained proper direction and warning if the manufacturer complied with the applicable regulations. However, a plaintiff may overcome the presumption by clear and convincing evidence that the manufacturer failed to use due care despite its compliance. *Patten*, 655 F.Supp. at 749. The *Patten* court concluded that because "the act was intended to increase the barriers to recovery of damages, it is fair to assume that Congress believed that the presumption it created did not exist under pre-Act law." 655 F.Supp. at 749. In this regard, it was stated in the legislative history "the establishment of these standards are the only new requirements that affect State law regarding actions for vaccine-related injuries or death; all other aspects of State law remain unchanged." 1986 U.S. Code Cong. & Admin. News at 6366.

In sum, in enacting the NCVIA Congress *clearly* evidenced a willingness to allow state tort remedies for vaccine-related injuries, despite broad federal regulation, and despite the manufacturers' compliance therewith.

The defendant argues that the enactment of the NCVIA is just another indication of congressional intent to control *every* aspect of prescription biologics: "The national interest in regulating the production of these vital medicines is so complete that Congress recently passed a Bill which bars civil actions based on injuries allegedly associated with federally regulated and state mandated vaccines. . . ." (Def.'s Memo. in Support of Motion for Summ. Judg. at 17.) In light of this court's previous discussion of the NCVIA, it is sufficient to state simply that defendant's argument is untenable.

Defendant also relies on the *Hurley* decision, previously cited, wherein the Eastern District Court of Texas found an implied congressional intent to preempt state tort actions. *Hurley* also involved the DPT vaccine. Defendant urges this court to find, as did the *Hurley* court, that: (1) the comprehensive nature of the FDA regulations evidences preemptive intent; (2) the nature of the DPT design and labeling relegates exclusive federal regulation in order to achieve uniformity vital to federal and national interests; and (3) state regulation (in the form of state tort remedies) would seriously and irreconcilably conflict with the federal statutory and regulatory scheme.

The court finds the *Hurley* decision unpersuasive for two reasons. First, and primarily, the Texas court did not refer to the NCVIA, and thus did not address or discuss Congress' clear statements found in the legislative history of that Act. Second, this court cannot agree that state tort remedies "conflict with" the regulatory scheme. While the *Hurley* court found that "a state common law determination that DPT design and manufacture is defective will seriously and irreconcilably conflict with the federal regulatory scheme and the national policies of immunization, adequate protection and supply of DPT" and "in effect will chill the efforts of the federal government to ensure that all U.S. children

are immunized and frustrate Congress' intent in fostering such programs," 651 F.Supp. at 1006, this court believes to the contrary that by allowing a tort action such as this to proceed the national goal of optimum vaccine safety is actually enhanced. While Congress intends vaccines to be at least as uniformly safe as the FDA regulations require, there has never been a congressional intent that innocent victims of adverse reactions should be precluded from being compensated or from demonstrating that the vaccines could be even safer thereby encouraging additional efforts on the part of the vaccine manufacturers.[5] Uniformity is a goal to be achieved in the interest of more fully protecting citizens from unsafe products—it is *not* to be achieved by sacrificing public health. However, the *Hurley* court held that uniformity was the ultimate goal in any case, stating, "[t]his decision is not to be construed to mean necessarily that defendants' DPT vaccine is not defective in fact, or that defendants' actual method of production is free from scrutiny. The court's holding merely finds that federal law as to defendants' design and labeling of DPT preempts plaintiffs' state tort claims in this respect." Such a holding is, in effect, an abrogation of traditional tort law.

In addition to *Hurley,* defendant cites only two other cases where courts have found federal preemption of DPT vaccine victims' tort claims. *See Abbot v. American Cyanamid,* No. 86-857-A (E.D.Va. Mar. 9, 1987); and *Morris v. Parke-Davis & Co.,* No. 82-5296-RJK (C.D.Cal. Sept. 19, 1985) [Available on WESTLAW, DCT data-base]. However, the *Morris* court has since withdrawn its finding of preemption, and entered a new order finding no preemption. *Morris v. Parke-Davis & Co.,* 667 F.Supp. 1332 (C.D.Cal.1987). The majority of

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5. The right to bring such lawsuits takes on added significance in view of the fact that most states, including Kansas and Missouri, require children to be immunized prior to attending public schools. The states have a great interest in compensating children who are victims of the vaccines and encouraging drug manufacturers to provide the safest possible vaccines.

federal courts which have considered this issue have found there is no implied preemption of state tort remedies. *See Patten,* 655 F.Supp. 745 (thoroughly discusses the NCVIA and finds it evidences congressional intent *not* to preempt); *Smith v. Wyeth Laboratories,* No. 84-2002 (S.D.W.Va. Aug. 21, 1986); *Jeski v. Connaught Laboratories,* No. A-84-CA-395, (W.D.Tex. Dec. 18, 1986); *Milam v. American Cyanamid,* No. 4-85-92-K (N.D.Tex. Oct. 15, 1986).

For the reasons stated, this court concludes that plaintiffs' claims are not preempted by federal law.

II. The Application of Kansas Law

Defendant argues that under Kansas law as stated in *Johnson v. American Cyanamid,* 239 Kan. 279, 718 P.2d 1318 (1986), it is entitled to summary judgment as to each of plaintiffs' claims. Defendant argues that in cases involving prescription biologics, which by their nature are "unavoidably unsafe," the public policy of Kansas, as set forth in *Johnson,* requires that such products be immune from challenge in the courts for defects in design. Defendant further argues that, pursuant to *Johnson,* this court must find the warning adequate as a matter of law.

In *Johnson,* the plaintiff contracted polio after his young daughter received her polio vaccine. Although the manufacturer, defendant Lederle Laboratories, knew such a consequence was possible, the plaintiff was never warned of this possibility. The doctor, who was also a named defendant at the trial level, had been advised by Lederle as follows:

> Paralytic disease following the ingestion of live poliovirus vaccines has been reported . . . in some instances, in persons who were in close contact with subjects who had been given live oral polio virus vaccine. Fortunately, such occurrences are rare. . . .

> The estimated risk of vaccine-induced paralytic disease occurring in vaccinees or those in close contact with vaccinees is extremely low. A total of approximately 30 of such cases were reported for the 8 year period covering 1963 to 1970, during which time 147,000,000 doses of the vaccine were distributed nationally.

239 Kan. at 288, 718 P.2d 1318.

The plaintiff brought an action in state court for design defect and failure to warn. The jury found no liability on the part of the plaintiff or the defendant doctor. The jury found defendant Lederle liable on all claims, awarding $2 million in actual damages and $8 million in punitives.

On appeal, the Kansas Supreme Court, in a 4-3 decision, reversed the verdict in its entirety, finding *no* liability on the part of Lederle. The court first discussed the history of the polio vaccine in some detail. As noted by the court, there are only two types of polio vaccines in existence—the Sabin vaccine and the Salk vaccine. The Sabin vaccine—which uses a live virus—was developed later than the "killed" Salk vaccine, and is the only type used in this country today. The court noted that the Salk vaccine is somewhat less efficacious than the Sabin vaccine, and that "[v]irtually all of the Western world utilizes the Sabin vaccine over the Salk vaccine in its public health programs." 239 Kan. at 283, 718 P.2d 1318. Nevertheless, the plaintiff had contended that defendant Lederle was strictly liable for design defect by virtue of using the Sabin-type vaccine rather than the Salk-type vaccine.

In finding the defendant free from *strict liability* on the design defect claim, the Kansas court adopted comment k to Section 402A of the Restatement (Second) of Torts. Comment k provides:

> k. *Unavoidably unsafe products.* There are some products which, in the present state of human

> knowledge, are quite incapable of being made safe for their intended and ordinary use. These are especially common in the field of drugs. An outstanding example is the vaccine for the Pasteur treatment of rabies, which not uncommonly leads to very serious and damaging consequences when it is injected. Since the disease invariably leads to a dreadful death, both the marketing and the use of the vaccine are fully justified, notwithstanding the unavoidably high degree of risk which they involve. Such a product, properly prepared, and accompanied by proper directions and warning, is not defective, nor is it *unreasonably* dangerous. The same is true of many other drugs, vaccines, and the like, many of which for this very reason cannot legally be sold except to physicians, or under the prescription of a physician. It is also true in particular of many new or experimental drugs as to which, because of the lack of time and opportunity for sufficient medical experience, there can be no assurance of safety, or perhaps even of purity of ingredients, but such experience as there is justifies the marketing and use of the drug notwithstanding a medically recognizable risk. The seller of such products, again the qualification that they are properly prepared and marketed, and proper warning is given where the situation calls for it, is not to be held to strict liability for unfortunate consequences attending their use, merely because he has undertaken to supply the public with an apparently useful and desirable product, attended with a known but apparently reasonable risk.

The Kansas Supreme Court found that the Sabin-type polio vaccine is "unavoidably unsafe" and entitled to comment k immunity as a matter of law. The court noted that "[t]he remote risk of contact polio is inherent in the Sabin-type vaccine and cannot be eliminated," but

that it is an "apparently useful and desirable product attended with a known but apparently reasonable risk." 239 Kan. at 285-86, 718 P.2d 1318. The court observed that "[t]he trial judge should have heard the evidence on the issue of [comment k's application] outside the presence of the jury and made the determination thereon." 239 Kan. at 286, 718 P.2d 1318.

Having concluded that as a matter of law the defendant could not be held strictly liable for a defect in design, the court reasoned "this leaves only the possible liability of the adequacy of the warning provided by the manufacturer." *Id.* In this regard, the court first observed the drug manufacturer's duty is "to adequately warn the physician of a known risk." *Id.* (citing *Wooderson v. Ortho Pharmaceutical Corp.*, 235 Kan. 387, 681 P.2d 1038. Because the test used in determining warning issues is "reasonableness", the court reasoned that the plaintiff must show *negligence* on the part of the manufacturer. The court quoted at length from *Kearl v. Lederle Laboratories,* 172 Cal.App.3d 812, 218 Cal.Rptr. 453 (1985), in support of this proposition. In *Kearl,* the court found that "[j]ust as liability for failure to warn of product risk is based on negligence, the adequacy of a warning is also judged under a reasonableness standard. . . ."

The *Johnson* court began its analysis of the warning by noting that the plaintiff's doctor had been warned of the precise "adverse reaction" from which plaintiff suffered: "This, then, is not a failure to warn question, but rather a question of the adequacy of the warning." 239 Kan. at 288, 718 P.2d 1318. The court then analyzed and rejected each of plaintiff's arguments for finding the warning inadequate. In effect, the court reweighed the evidence presented at trial. The court found that nothing in the warning was misstated ("plaintiff did not challenge [the risk figures given] directly"), or omitted ("the warning clearly states the scientific fact that some persons in close contact with vaccines may develop a

paralytic disease from such contact. . . . It hardly takes a medical degree to know that a person immune to the virus cannot acquire the disease."). *Id.* at 288, 289, 718 P.2d 1318. An additional factor which the court noted in finding the warning adequate was that "[t]he warning given . . . had been approved by the Federal Drug Administration and was consistent with an overwhelming bulk of the current medical opinion." *Id.* at 289, 718 P.2d 1318. The court concluded that the warning was adequate as a matter of law, and that the trial court erred by failing to direct a verdict in defendant's behalf.

The dissent took issue with the majority's finding that the warning was adequate as a matter of law, challenging the court's right to reweigh evidence or pass on the credibility of witnesses. 239 Kan. at 291-303, 718 P.2d 1318 (Prager, J., dissenting).

A. Design Defect

The defendant argues that in *Johnson* the Kansas Supreme Court held that *any* prescription biological vaccine is "unavoidably unsafe" as matter of law, and thus this court must find Wyeth free from liability for design defect. In this court's view, however, the *Johnson* decision is not—nor is it intended to be—so far reaching.

In *Johnson,* the Kansas Supreme Court adopted comment k to Restatement (Second) of Torts §402A. Section 402A imposes ***strict liability*** on a product manufacturer "who sells any product in a defective condition unreasonably dangerous to the user. . . ." Strict liability differs from negligence in that it obviates the need to show the manufacturer acted unreasonably, or, in other words, that he knew or should have known of the risk posed by the product. Strict liability in a products case focuses only on whether the product was defective, thereby imputing knowledge of the defect to the manufacturer.

[12] Comment k recognizes that some products, such as certain drugs, are so beneficial and necessary that the manufacturer of these products should not, in all instances, be held strictly liable for unforeseeable harm. "Society wishes to encourage the manufacture of ethical drugs, and the research and development of new drugs. The imposition of strict liability would stifle these goals." Schwartz, *Unavoidably Unsafe Products: Clarifying the Meaning and Policy Behind Comment K,* 42 Wash. & Lee L.Rev. 1139, 1141 (1985). Under comment k, if the drug is shown to be "unavoidably unsafe" (i.e., highly beneficial, yet inherently and unavoidably risky), the manufacturer cannot be held strictly liable for design defect *unless* the vaccine is improperly manufactured or contains an inadequate warning. Neither comment k nor *Johnson* stands for the rule that *all* prescription drugs are unavoidably unsafe as a matter of law. *See Toner v. Lederle Laboratories,* 732 P.2d 297, 308 ("We do not believe comment k was intended to provide nor should it provide all ethical drugs with blanket immunity from design defect claims. . . . [N]ot all drugs are so perfectly designed that they cannot be made more pure or more safe, or that there are not safer, suitable alternatives."); *contra Morris v. Parke-Davis & Co.,* No. 82-5296 (C.D.Calif. Sept. 19, 1985) [Available on WESTLAW, DCT database]. *Johnson* addressed only the Sabin-type polio vaccine, finding that particular vaccine to be unavoidably unsafe. In doing so, the court considered that while there was evidence of a somewhat safer alternative (the Salk-type vaccine), this alternative was not as efficacious. The court clearly recognized that whether or not the vaccine was "unavoidably unsafe" was an issue needing resolution ("[t]he trial judge should have heard the evidence on this issue outside the presence of the jury and made the determination thereon"), and not simply a tautology. Thus, the court did *not* find that drugs by definition are unavoidably unsafe.

The *Kearl* decision, cited with approval in *Johnson,* suggests the following approach in determining whether a given drug is unavoidably unsafe:

> In our view, the decision as to whether a drug, vaccine, or any other product triggers unavoidably dangerous product exemption from strict liability design defect analysis, poses a mixed question of law and fact and can be made only after evidence is first taken, out of the jury's presence, on the relevant factors to be considered. [Citations omitted.] A trial court should take evidence as to: (1) whether, when distributed, [footnote omitted] the product was intended to confer an exceptionally important benefit that made its availability highly desirable; (2) whether the then-existing risk posed by the product both was "substantial" and "unavoidable"; and (3) whether the interest in availability (again measured as of the time of distribution) outweighs the interest in promoting enhanced accountability through strict liability design defect review. In determining the first aspect of the second factor (i.e., whether the risk posed was substantial") a court should consider whether, at the time of distribution, the risk posed permanent or long-term disability (e.g., loss of body functions, organs, or death) as opposed to mere temporary or insignificant inconvenience (e.g., skin rash, minor allergic reaction, etc.). In determining the second aspect of the second factor (i.e., whether the risk posed was "unavoidable") a court should consider (i) whether the product was designed to minimize—to the extent scientifically knowable at the time it was distributed—the risk inherent in the product, and (ii) the availability—again, at the time of distribution—of any alternative product that would have as effectively accomplished the full intended purpose of the subject product.

218 Cal.Rptr. 453, 464. *See also, Toner v. Lederle Laboratories,* 732 P.2d 297, 305-09 ("Clearly, the comment contemplates a weighing of the benefit of the product against its risk . . . the weighing must be done at the time the product is distributed to the plaintiff. . . . [T]he design must be as safe as the best available testing and research permits. . . . Knowledge of the product's risks based on reliable and obtainable information is imputed to the seller.").

[13,14] This court is convinced that such factors *must* be considered before a court can determine whether a given drug falls within comment k's protection. In this case, the issue cannot be resolved as a matter of law at the summary judgment stage. Although defendant contends the whole cell DPT vaccine posed an *unavoidable* risk of severe injury, this is hotly contested by plaintiffs. Plaintiffs have submitted the affidavit of one of their experts, a Dr. Zahalsky, who will testify that Wyeth had the capability to produce a safer vaccine. Plaintiffs claim that Wyeth's own records substantiate this contention. Accordingly, there is an issue of material fact as to whether the "unsafety" of the DPT vaccine manufactured by Wyeth was unavoidable.

[15] Even if this court had concluded—or were eventually to conclude—that the vaccine is "unavoidably unsafe," the plaintiffs could still pursue their design defect claim under a negligence theory. Syllabus ¶ 1 to *Johnson* states:

> Although in standard products liability litigation plaintiff may utilize a strict liability design defect theory, such strict liability cause of action must be prohibited for public policy reasons where the product complained of is an unavoidably unsafe product within the purview of comment k to § 402A of Restatement (Second) of Torts (1963). *In such special circumstances, plaintiff may proceed on a design defect theory only on the basis of negligence.*

It is noteworthy that in the body of the opinion, *negligent* design defect is never mentioned or discussed, although this court understands it was a theory pursued at trial level. While the court is aware that Kansas is not a "syllabus state") i.e., the body of the case, not the syllabus, controls in case of conflict), the court is also aware that the Kansas Supreme Court justice who authors an opinion also writes its syllabus. Thus, while negligent design defect was not directly addressed in *Johnson,* there is at least limited authority—contained in the syllabus—that finding a drug to be "unavoidably unsafe" does not preclude the jury from considering the manufacturer's reasonableness. Quite clearly, by comment k's own terms, the comment bars only strict liabilty claims—i.e., that the product was "defective" and "unreasonably dangerous." Specifically, the comment states that the manufacturer of an "unavoidably unsafe" product is not to be held to *strict liability.* . . ." (Emphasis added.) The cases which have addressed the issue are in agreement that even though a product is deemed "unavoidably unsafe," the plaintiff may proceed under a negligence cause of action. *Toner,* 732 P.2d at 310,[6] *Kearl,* 218 Cal.Rptr. at 465; *Feldman v. Lederle Laboratories,* 479 A.2d 374, 381; *Stone v. Smith, Kline & French Laboratories,* 447 So.2d 1301, 1303 (Ala.1984). Accordingly, this court must conclude that comment k's application does *not* shield the seller of a product from negligence claims. Such a result fits within the policy of comment k—i.e., by denying plaintiffs recovery based on finding the manufacturer strictly liable if the drug is

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6. The Idaho Supreme Court heard the *Toner* case on questions certified from the Ninth Circuit Court of Appeals, including: Under Idaho law, do the principles set forth in Restatement (Second) of Torts § 402A comment k, apply to strict liability and negligence claims, and in particular to the claims in this suit? 779 F.2d 1433. Thus, the Idaho court's finding that comment k does not preclude the assertion of a claim for negligent design defect is-in effect-the law of the Ninth Circuit.

dangerous, and requiring the plaintiff to prove *negligence,* the policy of encouraging the production and marketing of safe, useful products is furthered.

Of course, the inquiry into whether a manufacturer acted negligently is, in a general sense, similar to the comment k inquiry of whether a drug is unavoidably unsafe. *Toner,* 782 P.2d at 310; *Feldman,* 479 A.2d at 385-86. Thus, in a case such as this where both theories (strict liability and negligence) are asserted, the evidence from which the court must determine if the product is unavoidably unsafe need *not* be heard outside the presence of the jury as it will be the *same* evidence from which the jury will determine negligence.

B. Adequacy of Warning

[16] Even if the evidence in this case shows that Wyeth used the best available vaccine and the product was "unavoidably unsafe," it will not be entitled to comment k immunity if it did not provide an adequate warning.[7] *Johnson,* 239 Kan. at 286, 718 P.2d 1318; *see also Brochu v. Ortho Pharmaceutical Corp.,* 642 F.2d 652, 657 (1st Cir.1981); *Reyes v. Wyeth Laboratories,* 498 F.2d 1264, 1276 (5th Cir.), *cert. denied,* 419 U.S. 1096, 95 S.Ct. 687, 42 L.Ed.2d 688 (1974); *Davis v. Wyeth Laboratories, Inc.,* 399 F.2d 121, 128-29 (9th Cir.1968); *Yarrow v. Sterling Drug, Inc.,* 263 F.Supp. 159, 163 (D.S.D.1967), *aff'd.,* 408 F.2d 978 (8th Cir.1969); *Toner v. Lederle,* 732 P.2d at 305; *Kearl,* 218 Cal.Rptr. 465. The comment thus recognizes that while some products are inherently dangerous, the user has a right to know of these inherent risks so that he can make an informed decision; in the absence of such warning, the product is deemed to be defective.

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7. Because Mrs. Graham was warned that brain damage could result from the vaccine, the issue before the court is not *failure* to warn, but rather, *adequacy* of the warning. *See Johnson,* 239 Kan. at 288, 718 P.2d 1318.

An adequate warning is one that is reasonable under the circumstances. *Wooderson v. Ortho Pharmaceutical Corp.*, 235 Kan. 387, 400, 681 P.2d 1038. A warning may be inadequate in factual content, the expression of facts, or in the method by which it is conveyed. *Id.* In the case of mass innoculations, vaccinees must be informed,[8] in clear and simple terms, by the manufacturer of: (1) the reasonably foreseeable risk inherent in the product; (2) reasonable available alternative products (if any) and the reasonably foreseeable risks posed by such alternatives; and, in appropriate cases, (3) the reasonably foreseeable results of remaining untreated. *See Johnston*, 239 Kan. at 292, 718 P.2d 1318 (Prager, J., dissenting); *Unthank v. United States*, 732 F.2d 1517, 1521 (10th Cir.1984). The manufacturer's duty is to warn of all potential dangers which it knew, or in the exercise of reasonable care should have known, to exist. This duty is a continuous one, requiring the manufacturer to keep abreast of the current state of knowledge. *Wooderson*, 235 Kan. at 405, 681 P.2d 1038.

[17] To impose liability on the defendant for inadequate warning, the plaintiff must show *negligence* on the part of the manufacturer. *Johnson*, 239 Kan. at 286, 718 P.2d 1318. Accordingly, plaintiffs are precluded from

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8. Generally, in the case of prescription drugs, the manufacturer's duty is to adequately warn the physician of known risks. *Johnson*, 239 Kan. at 286. This is known as the "learned intermediary" rule. However, there is authority that when a vaccine is dispensed at a clinic without close supervision by a physician, the manufacturer's duty to warn extends to the vaccinee. In *Johnson*, the vaccine was administered by a doctor, and the court found that "under such circumstances" the learned intermediary rule applied. In the case at bar, the vaccine was administered by a nurse at a clinic. However, the plaintiffs herein seem to assume the learned intermediary doctrine applies.

In any event, a manufacturer is directly liable to the patient when the warning to the "learned intermediary" is inadequate. *Wooderson*, 235 Kan. at 400, 681 P.2d 1038.

asserting a claim of strict liability for failure to warn and summary judgment will be entered for defendant on that claim.

[18] Defendant argues that the warning given was adequate as a matter of law. In this regard, defendant urges the court to find that *Johnson* is directly on point and *requires* a finding of adequate warning. This court cannot agree.

Johnson must necessarily be limited to its facts on the warning issue. As previously stated, the adequacy of a warning turns on its reasonableness *under the circumstances*. The *Johnson* court found that under the circumstances before it, reasonable minds could not differ on the adequacy of the warning. *Johnson* does nothing to change the factual nature of the inquiry.

It is well established in Kansas that whether a warning is adequate is an issue for the trier of fact. *Wooderson,* 235 Kan. at 409, 681 P.2d 1038. Moreover, the testimony of experts in the field should be considered. *Siruta v. Hesston Corp.*, 232 Kan. 654, 659 P.2d 799 (1983).

In this case the plaintiffs will offer evidence that the warning misstated the statistical incidence of severe reactions, failed to adequately identify the level of endotoxin in each vial or lot, and failed to state that persons with a family or personal history of seizures or central nervous system disorders should forego immunization and seek further medical evaluation prior to vaccination. Although defendant adamantly challenges these allegations, these are clearly issues which must be resolved by the trier of fact.

Defendant further argues that the court should find it non-negligent *per se* as the warning given had been approved by the FDA. However, as previously stated, FDA standards are *minimum* standards. While the FDA's approval is a factor to be considered by the jury, it does not establish non-negligence *per se*. The *Johnson* decision is not to the contrary: the FDA's approval of the

warning was only one of the several factors it considered in finding the warning adequate as a matter of law.

Finally, the defendant argues that this court must grant summary judgment on the warning claim because the inadequacy of the warning was not the proximate cause of Michelle Graham's injuries. In this regard, defendant asserts that Mrs. Graham based her decision to have her baby immunized *solely* on the nurse's remarks indicating that she had no other choice.

However, the defendant's argument fails to recognize the rule that if a jury finds a warning inadequate, causation is presumed. *Wooderson*, 235 Kan. at 410, 681 P.2d 1038. In other words, it is presumed that an adequate warning would be heeded by the patient. *Id.* Thus, in this case, if an adequate warning had been given (assuming arguendo that the one given was inadequate), it is possible the nurse would have not said the things she did, or perhaps would have suggested alternatives. This, though, is a matter of pure speculation; hence, the presumption.

The defendant argues the fact that Mrs. Graham initially hesitated because of her concern with adverse reactions proves the warning she received was adequate. This—again—is entirely speculative. While such evidence is certainly admissible, it does not require a finding that the warning was adequate as a matter of law. In fact, it begs the question of whether Mrs. Graham would have consented to the vaccine if the warning had contained all that plaintiffs contend it should have.

Accordingly, the issue of the warning's adequacy is factual and must be resolved by the trier of fact.

C. Breach of Warranty and Misrepresentation

[19] Because the court does not grant summary judgment on the plaintiff's tort claims, the warranty claims—at this point—are merely superfluous. As such,

the court will deny defendant's motion for summary judgment as to these claims for the same reason set forth above. In doing so, the court notes that by filing this lawsuit the defendant was given sufficient notice, under K.S.A. 84-2-607, of the alleged breach of warranty. *See Owens v. Glendale Optical Co.*, 590 F.Supp. 32 32 (S.D. Ill.1984); *Palmer v. A.H. Robins Co., Inc.*, 684 P.2d 187 (Colo.1984); *Goldstein v. G.D. Searls & Co.*, 62 Ill.App.3d 344, 19 Ill.Dec. 208, 218, 378 N.E.2d 1083, 1089 (1978).

As to the misrepresentation claim, the defendant argues only that plaintiffs are unable—as a matter of law—to show *reliance*. As previously discussed with regard to the adequacy of the warning, it is presumed that additional warnings (or representations) would have been heeded. Thus, the defendant's argument is without merit.

III. Conclusion

Vaccines such as the DPT vaccine play an important and critical role in this society. Millions of lives are saved. However, some innocent people—such as Michelle Graham—are grievously injured by these vaccines. The defendant has argued that the doctrine of federal preemption precludes victims from seeking compensation from the vaccine manufacturers. However, this court finds that Congress did not intend to preclude vaccine victims from bringing state tort lawsuits. The fact that the vaccine manufacturer complied with FDA regulations is evidence that should be considered by a jury; however, these regulations set minimum standards. Manufacturers are *not* precluded from taking steps to improve their vaccine, or to better inform as to its dangerous propensities. In this case, the evidence must be heard before it can be determined that the whole cell vaccine was the safest and most efficacious

available—in other words, that it was "unavoidably unsafe." And in any case, the adequacy of the warning is an issue for the trier of fact. Thus, this court will not rule that as a matter of law Michelle Graham will be denied any recourse. This case will proceed to trial.

IT IS ACCORDINGLY ORDERED this 21 day of July, 1987, that defendant's motion for summary judgment is granted as to plaintiffs' claim of strict liability for failure to warn, and is denied as to all remaining claims.

ORDER NUNC PRO TUNC

In its Memorandum and Order of July 21, 1987, denying defendant's motion for summary judgment, the court applied the law of the State of Kansas. This was done due to the parties' stipulation, contained in the pretrial order, that the law of Kansas would apply, even though the infant plaintiff received her vaccination in the State of Missouri.

APPENDIX C

IN THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF KANSAS

MICHELLE GRAHAM, an Infant Under the Age of Eighteen, Who Sues By Her Parents, Guardians and Next Friends, Charles Graham and Tammy Graham, *Plaintiff,*	)	
vs.	)	No. 85-1481-K
WYETH LABORATORIES, a Division of American Home Products Corporation, a Pennsylvania Corporation, *Defendant.*	)	

VERDICT

We, the jury, being duly impaneled and sworn, submit the following answers to the special interrogatories propounded by the court:

1. Does the Wyeth whole cell DTP vaccine cause or substantially contribute to the cause of encephalopathy in children?

Yes ✓ No __

[If you answer No. 1 "yes", please proceed to answer No. 2; if you answer No. 1 "no", have your foreperson sign and date this verdict form and notify the bailiff that you have concluded your deliberations.]

2. Does the DTP vaccine received by Michelle Graham on March 17, 1980, cause or substantially contribute to the cause of her encephalopathy?

Yes ✓ No __

[If you answer No. 2 "yes", please proceed to answer No. 3; if you answer No. 2 "no", have your foreperson sign and date this verdict form and notify the bailiff that you have concluded your deliberations.]

3. In March of 1980, was defendant Wyeth negligent in connection with testing, designing and/or warning in regard to its DTP whole cell vaccine, which was the legal cause of plaintiff's injuries?

Yes ✓ No _

4. In March of 1980, was the DTP whole cell vaccine manufactured by Wyeth in a defective condition unreasonably dangerous to persons as a result of its design, which was the legal cause of plaintiff's injuries?

Yes ✓ No _

5. In March of 1980, was the DTP whole cell vaccine in a defective condition unreasonably dangerous to persons as a result of inadequate warnings, which was the legal cause of plaintiff's injuries?

Yes ✓ No _

[If your answer is "yes" to Nos. 3, 4 *or* 5, proceed to next question; if your answer is "no" to Nos. 3, 4 *and* 5, then have your foreperson sign and date this verdict form and notify the bailiff that you have concluded your deliberations.]

6. What is the total amount of damages sustained by the plaintiffs as a result of the injuries to Michelle Graham?

$15 million

Oct. 14, 1987
Date

XXX
Foreperson

APPENDIX D
No. 88-1337

IN THE UNITED STATES COURT OF APPEALS
FOR THE TENTH CIRCUIT

MICHELLE GRAHAM, ***et al.,***
Plaintiffs-Appellees,

v.

WYETH LABORATORIES, *etc.*
Defendant-Appellant.

ON APPEAL FROM THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF KANSAS

BRIEF FOR THE UNITED STATES AS AMICUS CURIAE

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TABLE OF CONTENTS

Page

Interest of the United States..... [84a]

Introduction ..... [84a]

Discussion..... [86a]

1. History and Epidemiology of Pertussis ..... [87a]
2. Development of the Whole Cell Pertussis Vaccine..... [88a]
3. Other Vaccines..... [91a]
   (a) Extracted Vaccines..... [92a]
   (b) Acellular Vaccines ..... [94a]
4. The Federal Role ..... [98a]

Conclusion ..... [103a]

Certificate of Service ..... [104a]

TABLE OF AUTHORITIES

Cases: *Page*

White v. Wyeth Laboratories, Inc., Nos. 52108 & 52564 (Court of Appeals of Ohio, Eighth District, July 30, 1987) ..... [88a]

Loveday v. Renton and Another, No. 1982 L 1812 (Queen's Bench) (March 30, 1988) ..... [88a]

Statutes and Regulations:

Vaccination Assistance Act of 1962, 42 U.S.C. § 247b ..... [98a]

50 Fed. Reg. 51040-42 (1985) ..... [83a]

50 Fed. Reg. 51051-51052 ..... [90a]

Miscellaneous:

"Acellular and Whole-Cell Pertussis Vaccines in Japan," *Journal of the American Medical Association* (March 13, 1987) ..... [86a-92a]

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Himan and Koplan, *Pertussis and Pertussis Vaccine: Reanalysis of Benefits, Risks, and Costs,* Journal of the American Medical Association (June 15, 1984) ..... [85a, 89a]

Kallings, Olin and Storsaeter, *Placebo-Controlled Trial of Two Acellular Pertussis Vaccines in Sweden Protective Efficacy and Adverse Events,* The Lancet (April 30, 1988) ... [92a, 96a]

Manclark & Cowell, "Pertussis" in Germanier (ed.), *Bacterial Vaccines* (1984) ..... [86a, 88a, 89a]

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United States Department of Health and Human Services, "Pertussis and Pertussis Vaccines in Japan" (May, 1986)..... [89a]

IN THE UNITED STATES COURT OF APPEALS
FOR THE TENTH CIRCUIT

No. 88-1337

MICHELLE GRAHAM, *et al.*,
Plaintiffs-Appellees,

v.

WYETH LABORATORIES, *etc.*,
Defendant-Appellant.

ON APPEAL FROM THE UNITED STATES
DISTRICT COURT
FOR THE DISTRICT OF KANSAS

BRIEF FOR THE UNITED STATES AS AMICUS CURIAE

INTEREST OF THE UNITED STATES

The United States submits this *amicus curiae* brief on behalf of the Department of Health and Human Services (HHS), which maintains a longstanding national program to vaccinate all American children against pertussis, or "whooping cough." The purpose of this brief is to provide the Court with background information concerning the federal government's role in pertussis vaccination. The United States expresses no opinion on the question whether federal law preempts plaintiff's state tort remedies in this case.

INTRODUCTION

Federal public health authorities, including the Food and Drug Administration (FDA), the Centers for Disease Control (CDC), the National Institutes of

Health (NIH), and other agencies, have, for almost forty years, promoted vaccination of the populace with diphtheria-tetanus-pertussis (DTP) vaccines containing as one of their three components the so-called "whole cell" pertussis vaccine.[1] These agencies have supported use of this "whole cell" component because of its proven value for millions of children, even though they recognize that some observers have, in the past, claimed that a small number of those vaccinated could suffer serious, adverse side effects. These agencies are unaware of any other pertussis vaccine produced in the world today that has been adequately demonstrated to be both safer than and as effective as the "whole cell" vaccine licensed for sale by the FDA.

Pertussis is a serious disease which is most dangerous to its youngest victims. Before the introduction of the "whole cell" vaccine, pertussis disabled and killed thousands of children annually in the United States. After more than 40 years of widespread use of that vaccine in this country, the disease has been brought largely under control. Pertussis remains a significant cause of infant deaths, however, in some other parts of the world which lack such vaccination programs.[2] Moreover, the bacterium causing the disease persists even where the disease is under control, as in this country. This leads to the probability of epidemics whenever the

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1. Technically, "whole cell" pertussis vaccines produced by different manufacturers are considered to be different vaccines even though they are of the same basic design and meet the same federal requirements. HHS believes that the "whole cell" vaccines produced by licensed manufacturers are equally acceptable, safe, and effective products. For ease of discussion, "whole cell" vaccines will be referred to in the singular throughout this brief.

2. See 50 Fed. Reg. 51040-42 (1985) (Report of the Panel on Review of Bacterial Vaccines and Toxoids) ("Panel Report"). This report, by a group of medical experts appointed by FDA to review the safety, efficacy and labeling of all bacterial vaccines, contains a thorough discussion of the disease, the development of the "whole cell" vaccine, and the vaccine's safety and efficacy.

use of the vaccine declines significantly. The responsible federal health agencies have consistently recommended that all children, excepting those with specific medical contraindications, be inoculated.

Charles and Tammy Graham, on their own behalf and on behalf of their child, Michelle, filed this suit in federal district court in Kansas. The defendant is Wyeth Laboratories, a division of American Home Products Corporation. Wyeth formerly manufactured a "whole cell" pertussis vaccine which it marketed as a part of a DTP vaccine.[3] The plaintiffs asserted that Michelle suffers from a seizure disorder and encephalopathy (a disease of the brain) caused by her DTP inoculation in 1980. Their suit alleged claims of strict liability, negligence and breach of implied warranties. The jury returned a verdict against Wyeth, awarding $15,000,000 in compensatory damages.

"Whole cell" pertussis vaccine is made from whole killed cells of *Bordetella pertussis,* the bacterial agent that causes the disease. The vaccine contains substances which plaintiffs claimed were capable of causing adverse reactions in vaccines. The plaintiffs here also contend that Wyeth could have and should have manufactured and sold a different type of pertussis vaccine less likely to cause adverse reactions.

DISCUSSION

HHS supports the continuing manufacture and marketing of the "whole cell" vaccine because no alternative formulation has been adequately proven to be both safer than and as effective as the "whole cell" vaccine. HHS's support for continued production of this

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3. Although it is still licensed to do so, Wyeth no longer manufactures or markets DTP. The only commercial suppliers of the vaccine in this country today are Connaught, Inc. and a division of American Cyanamid, Lederle Laboratories.

product is consistent with the vigorous recommendations of all sectors of the medical community, both public and private, which have carefully analyzed the dangers of the disease and the benefits and risks associated with the vaccine.

Experts still have not determined what part of the whole *B. pertussis* cell used in the "whole cell" vaccine provides immunity to the recipient. HHS, the governments of other nations, and numerous private firms are actively seeking an improved vaccine that provides the protection of the "whole cell" design. Until the time that HHS is convinced that such an alternative vaccine has been found, it will continue to advocate the use of "whole cell" vaccine as a vital part of our nation's public health policy.

1. History and Epidemiology of Pertussis.

Pertussis, or whooping cough, is a highly contagious disease caused by *Bordetella pertussia,* a bacterium. Human beings are the only natural hosts of *B. pertussis,* and infected individuals are the primary sources of disease in susceptible persons. Transmission occurs via droplets from the respiratory tract which are expelled into the air by infected individuals. Up to 90% of nonimmune household contacts acquire the disease. *Report of the Committee on Infectious Diseases,* American Academy of Pediatrics (1986) ("The Red Book"). Later stages of the disease are characterized by severe and paroxysmal coughing which ends in a prolonged, high-pitched crow (the whoop) that is occasionally accompanied by vomiting. Recovery may take many weeks or months. The disease is most dangerous to infants and young children. During the years 1940-1948, the mean annual pertussis mortality rate for infants up to 12 months of age was 64 per 100,000 population, as compared with only 6.4 per 100,000 children ages 1 through 4, and 0.2 for children ages 5 through 14. Cherry, "The

Epidemiology of Pertussis and Pertussis Immunization in the United Kingdom and the United States: A Comparative Study," *Current Problems in Pediatrics* (1983) ("Cherry"), p. 18. Complications of pertussis include brain diseases, convulsions, partial lung collapse, secondary infections such as pneumonia, and permanent developmental retardation. See generally Manclark & Cowell, "Pertussis" in Germanier (ed.), *Bacterial Vaccines* (1984) ("Manclark & Cowell"), pp. 69-106.

In 1934, when this country suffered its worst pertussis epidemic, there were 265,000 reported cases of pertussis and 7,500 related deaths. Hinman and Koplan, *Pertussis and Pertussis Vaccine: Reanalysis of Benefits, Risks, and Costs,* Journal of the American Medical Association ("Hinman and Koplan") (June 15, 1984). By the early 1940s, pertussis was responsible for two and a half times the number of deaths as all of the following diseases combined: measles, mumps, rubella, diphtheria, polio, meningitis, chicken pox, and scarlet fever. While the use of pertussis vaccine has reduced the number of deaths attributable to pertussis to approximately 10 per year ("Recommendation of the Immunization Practices Advisory Committee (ACIP)," *Morbidity and Mortality Weekly Report,* ("MMWR") U.S. Dept. of H.H.S., July 12, 1985), the potential for epidemics is still present. Hinman and Koplan, p. 3113.

2. Development of the Whole Cell Pertussis Vaccine.

B. pertussis was identified as the cause of whooping cough in 1906 at the Brussels Pasteur Institute. The first vaccine against pertussis was licensed by the federal government in 1914. Additional developmental changes were made in the "whole cell" vaccine we know today starting in the 1920s. This research led to the development of experimental vaccines and clinical trials in the 1930s. In the early 1940s, pertussis vaccination

became widespread, and, in 1944, the Council on Pharmacy and Chemistry of the American Medical Association (AMA) accepted and endorsed pertussis vaccination. From 1943 to 1976 the country showed a 99% reduction in the reported cases of pertussis per 100,000 population, and an even more dramatic reduction in the number of deaths. Both the number of cases and deaths due to pertussis have remained constant since 1976. Cherry, pp. 11-12. CDC believes that, since 1980, 95 percent of all American children who have reached five years of age have received the complete course of immunization against pertussis.

In 1949, federal criteria governing the manufacturing process and potency testing of all batches of pertussis vaccine were developed. The same year the federal government licensed a combined product consisting of diphtheria and tetanus toxoids and "whole cell" pertussis vaccine and approved the product's labeling as well. This type of product is the familiar diphtheria-tetanus-pertussis (DTP) vaccine formerly produced by Wyeth.

According to the best information available to the government, of the ten companies that have at any time obtained licenses to manufacture or distribute DTP vaccine in this country, only two, Lederle and Connaught, Inc., continue to produce the vaccine.[4] The pertussis vaccine used by those firms, and by the two state health laboratories with licenses to produce a DTP vaccine, incorporate a "whole cell" pertussis component like that at issue in this lawsuit against Wyeth.

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4. SCLAVO, an Italian pharmaceutical firm, is licensed to manufacture and sell "whole cell" DTP vaccine in the United States but is not presently distributing its vaccine in this country. The Michigan and Massachusetts state health laboratories also have licenses from FDA to produce DTP vaccines for use in those states.

While it has been thought by some that the "whole cell" pertussis vaccine can be associated with rare, neurological reactions, other authorities in recent years have concluded that these reactions are unconnected with "whole cell" vaccinations.[5] However, clinical trials, 50 years of experience with the vaccine, and the great reduction in the number of reported cases of the disease and related deaths all demonstrate that, used properly, the "whole cell" pertussis vaccine is acceptably safe and very effective in controlling the disease. Manclark & Cowell, p. 84.[6]

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5. In a widely noted and exceptionally detailed opinion, a British court recently rejected the argument that "whole cell" vaccines cause neurological reactions. In *Loveday v. Renton and Another*, No. 1982 L 1812 (Queen's Bench) (March 30, 1988), the court heard a test case presenting the issue of whether "whole cell" pertussis vaccine could cause permanent brain damage (including encephalopathy) in young children. The plaintiff, a 17 year-old girl, sued Dr. Renton, the pediatrician who had administered the vaccine to her in 1970 and 1971, claiming that she suffered severe brain damage as the direct result of taking the vaccine. The only remaining British firm manufacturing pertussis vaccine, the Wellcome Foundation, intervened in the case although there was no claim of negligence against it. The trial lasted several months, during which time many of the world's leading medical authorities testified. In his decision, Lord Justice Stuart-Smith concluded that, on the basis of the evidence, the plaintiff had not proven that the "whole cell" vaccine causes brain damage in children. The court concluded that any correlation between vaccination and brain damage was attributable to the coincidence between two independent phenomena; (a) the minor, but observable, reactions (such as fevers) that sometimes accompany administration of the vaccine, and (b) rare, severe neurological problems that are noted at the same time in certain children's lives.

6. In a decision last year, an Ohio appellate court essentially agreed with this conclusion although, unlike the English court in the *Loveday* decision, it assumed that some risk was connected with use of the vaccine. *White* v. *Wyeth Laboratories*, Nos. 52108 and 52564, slip op. at 13. (Court of Appeals of Ohio, Eighth District, July 30, 1987) (on LEXIS). The *White* court held that Wyeth's DTP vaccine containing a "whole cell" pertussis component was an "unavoidably unsafe product" because it was "an apparently useful

The importance of inoculating children with "whole cell" vaccine is perhaps best demonstrated by reviewing what happened in the United Kingdom and Japan during the 1970s when the use of the vaccine declined. Because of public concern regarding the "whole cell" pertussis vaccine, the number of individuals immunized against pertussis in Britain dropped from 79 percent in 1973 to 31 percent in 1978. An epidemic of pertussis broke out between 1977 and 1980 that resulted in 102,500 cases of disease and 36 related deaths. In the winter of 1981-1982, approximately 1,400 cases of pertussis were reported each week to British public health officials. A total of 49,543 cases were reported during the first nine months of 1982 alone. Cherry, pp.36-39 and MMWR (December 3, 1982), p. 629. The Japanese had a similar experience when the use of the "whole cell" vaccine declined from approximately 70 percent in the early 1970s to approximately 30 or 40 percent in 1975. By 1979, the Japanese reported an epidemic of 13,105 cases of pertussis and 41 deaths. Manclark & Cowell, p. 94, and U.S. Department of Health and Human Services, "Pertussis and Pertussis Vaccines in Japan", May 9, 1986. CDC estimates that, under current conditions, if the use of "whole cell" pertussis vaccine were halted in this country, there would be 353,000 additional cases of disease and 450 deaths per year. Hinman and Koplan, p. 3112.

3. Other Vaccines.

It is the plaintiffs' theory in this case that Wyeth should be held liable because a design defect in the

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and desirable product, attended with a known but apparently reasonable risk." *Id.* The court concluded that "[p]ublic policy requires that the mere manufacture of the vaccine not be actionable on design defect grounds" and that the manufacturer was not liable for adverse reactions associated with the vaccine if adequate warnings of the risks were provided. *Id.*

"whole cell" vaccine made it unreasonably dangerous. They allege that trial testimony established that removing endotoxin from the vaccine was feasible, effective and increased the safety of the vaccine." Plaintiff's Opposition to Motion for Judgement N.O.V., p.12. According to the plaintiffs, other types of vaccines are as effective as the "whole cell" vaccine and are safer in that they cause fewer adverse reactions. See Plaintiff's Trial Brief at 22-23. The plaintiffs argued that Wyeth, instead of manufacturing a "whole cell" vaccine, should have developed, obtained FDA license approval for, and marketed in 1980 either an extracted cell or an acellular vaccine. *Id.* HHS is unconvinced that current evidence demonstrates that there are presently safer and equally effective alternatives to the "whole cell" vaccine.

(a) *Extracted Vaccines.* Eli Lilly and Company manufactured and marketed a DTP product called "Tri-Solgen" between 1962 and 1977 under an FDA-approved license. "Tri-Solgen" contained a pertussis vaccine component prepared from an extract of whole *B. pertussis* cells that was a complex mixture which differed from whole cells primarily by being soluble. The extracted pertussis component of "Tri-Solgen" passed the same laboratory tests for freedom from toxicity and for potency required for "whole cell" vaccines. The extracted vaccine was considered effective based upon the fact that it met the laboratory requirements for potency. However, no controlled clinical efficacy trials were ever performed on this vaccine comparable to those performed on "whole cell" vaccine in the 1940s and 1950s. Panel Report, 50 Fed. Reg. 51051-51052.

Following the decision by Eli Lilly to cease manufacture of "Tri-Solgen", Wyeth Laboratories, Inc., which was then producing a "whole cell" vaccine, took an option from Eli Lilly to produce a "Tri-Solgen"-type extracted pertussis vaccine. After considerable research, Wyeth produced its own extracted vaccine in the late

1970s and, in 1982, submitted a license application to the FDA to manufacture and sell a DTP vaccine containing such a pertussis component. The license application included research information, production data, and two small clinical trials evaluating immunogenicity (*i.e.*, capacity to confer immunity), as measured by antibody responses in children, and safety, as measured by adverse reaction information from all subjects tested. While there appeared to be fewer local and mild systemic reactions to the extracted vaccine than with "whole cell" vaccine, there were two severe reactions during the clinical tests – one episode of collapse and one episode of cyanosis – in the group receiving the extracted vaccine.

Wyeth's data were reviewed by FDA and by a panel of consultants convened by FDA. Based on the observation of the two serious reactions in children receiving the extracted vaccine and the fact that Wyeth's extracted vaccine has less potency than "whole cell" vaccine, they concluded that additional data would be necessary before a license could be issued.[7] While technically the application has not been withdrawn, it has remained inactive and no license has been issued for Wyeth's

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7. Because the performance characteristics of biological products depend on the manufacturer, the manufacturing process, the manufacturing facility, and other variables, vaccines made by different manufacturers are treated as separate products, even if they are of the same design and for the same purpose. Therefore, Wyeth could not simply make and sell "Tri-Solgen"; rather, Wyeth had to obtain the manufacturing technology from Lilly and develop its own extracted pertussis vaccine. Wyeth's vaccine was then subject to FDA evaluation without regard to the existing approval of Lilly's similar extracted pertussis vaccine. Although the Wyeth vaccine was not approved, it is not possible to conclude that "Tri-Solgen" was "better" than the Wyeth vaccine because different tests were done on the two vaccines.

extracted vaccine. In 1985, Eli Lilly voluntarily requested FDA to revoke its license to manufacture "Tri-Solgen," and the agency accordingly granted Lilly's request.

(b) *Acellular Vaccines.* Acellular pertussis vaccines differ from earlier vaccines in that they contain less endotoxin (a toxic substance produced by the pertussis bacterium). While the acellular vaccines, which are marketed by Japanese firms, have been reported to cause fewer mild to moderate reactions than the "whole cell" products, it is not clear whether they are as effective. Since 1981, the acellular vaccines have been used in the mass immunization program in Japan. Although the results with these vaccines are encouraging, additional clinical evaluation is deemed necessary to demonstrate safety and efficacy. One of the clinical trials being watched with great interest is that recently completed in Sweden. Changes made in the Swedish "whole cell" vaccine in the 1970s rendered that vaccine ineffective and its use was discontinued. As a result, Sweden has experienced a significant increase in the number of cases of pertussis in the years since 1974. The clinical trial of two Japanese acellular vaccines was designed by Swedish public health officials in close consultation with their American counterparts at FDA, NIH, and CDC, and the trial was funded in part by HHS and the U.S. Agency for International Development. Neither of the two vaccines tested in Sweden is licensed for use in the United States, and only one is approved for general use in Japan.

Some early information is now available concerning the Swedish clinical trial. See generally Kallings, Olin, and Storsaeter, *Placebo-Controlled Trial of Two Acellular Pertussis Vaccines in Sweden — Protective Efficacy and Adverse Events*, The Lancet (April 30, 1988) ("Kallings, *et al.*"). The study was designed as a classical

randomized, double-blind, placebo-controlled trial.[8] Sweden could be used as the location for this type of study for several reasons: there is a relatively high incidence of pertussis among Swedish children, the country's medical care system is advanced and equipped to handle the extensive follow-up and record-keeping functions such a study requires, and the Swedish health authorities do not recommend immunization against pertussus. Thus, investigators could ethically withhold both a vaccine known to be effective and acceptably safe (the "whole cell" vaccine) and a potentially useful experimental vaccine (acellular vaccines), and give a placebo instead. By comparison, HHS believes that it would be extraordinarily difficult to conduct such a study in the United States because there are so few cases of pertussis that it would take a trial including approximately 200,000 children to show any differences in safety or efficacy between the "whole cell" and acellular vaccines.

A total of 3,800 children, who were between the ages of six and nine months at the time of their first dose of vaccine, participated in the study in Sweden. All of the children received two doses of vaccine (or a placebo) which were given two to three months apart. Two acellular vaccines were used in the study, both produced in Japan. The two vaccines differ in that one is composed of equal parts of two pertussis antigens, while the other contains only one of the antigens. The double component product is one of the approximately six different acellular vaccines that the Japanese government has approved for use in its mass immunization

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8. In other words, in this trial the study population was randomly divided into three groups that were then given either of the two vaccines or an inert substance known as a placebo. Neither the scientists conducting the study nor the subjects knew which individuals received the two vaccines or which received the placebo. In such a double-blind study, only once the trial is complete and scientists are ready to analyze its results do they "break the code" to determine the effects of the vaccine.

program.[9] The single component vaccine is not, to the best of our knowledge, approved for general use in Japan at this time.

Data concerning adverse reactions which were reported in the children participating in the study, including the deaths of four of the children, are being evaluated. The deaths took place between two weeks and five months following the final injection of vaccine, and each was caused by or associated with a severe bacterial infection. Researchers broke the study codes, and it was determined that three of the children had received the two-component Japanese-approved vaccine. The fourth child was in the group that received the new single component product. Any deaths occurring in a study population this small are, of course, taken very seriously. Investigators do not yet know whether these deaths are related to the vaccines in any way and they are evaluating that possibility.

The formal analysis of the data amassed in this study — the first controlled efficacy study on any of the new acellular pertussis vaccines — began in the Fall of 1987, with the preliminary results published in early 1988. The data from this study demonstrate that the acellular pertussis vaccines are effective in providing some protection against the disease, although the efficacy rates of both vaccines were lower than had been expected. It appears that the acellular vaccines are effective approximately 50 percent of the time in preventing exposed recipients from contracting pertussis. By comparison, the whole cell vaccine has been demonstrated to be over 80 percent effective in preventing disease, with at least one study showing an efficacy rate of over 90 percent. Further, the study showed that the acellular vaccines both caused fewer mild local and

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9. Each of these vaccines is composed of different antigens in different ratios to each other. Each product is thus distinct and may have different safety and efficacy characteristics.

systemic reactions, such as swelling, redness, and fever, than does the whole cell vaccine. The Swedish clinical trial was too small, however, to determine the safety of the acellular vaccines in relation to rare, serious adverse events temporarily associated with inoculation. Kallings, *et al.*, pp. 958-960.

The Japanese put their acellular vaccines into widespread use in the absence of a controlled study demonstrating that each of the vaccines was effective in preventing pertussis. Thus, the impact of these acellular vaccines on the incidence of the disease in Japan is difficult to evaluate, according to some observers. Several small household or secondary attack rate studies had indicated that these products are generally effective, but little product-specific efficacy data are available for each of the Japanese vaccines. The Swedish clinical trial provided the first information from a controlled study about the effectiveness of modern-day acellular vaccines. While the efficacy data from the study are an important step forward, the results of the study are not as conclusive as researchers had hoped they would be and a number of important questions remain unanswered. Additional analyses of the data and neurological responses are planned. The study also demonstrated that designing a vaccine to fight a bacterial disease is much more complicated than scientists had realized. The World Health Organization has recommended that additional studies be performed, perhaps including as many as 100,000 children according to one estimate, to gather more information. See generally Marwick, *Pertussis Vaccines: Trials (and Tribulations)*, JAMA, April 8, 1988, pp. 2057-2059.[10]

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10. In addition, significant technical problems must be resolved before an acellular pertussis vaccine can be licensed for use in this country. Indeed, the last day of an international symposium on the development of acellular vaccines sponsored by the Department of Health and Human Services in September, 1986 was devoted to these issues. They include, among many others, the

The acellular vaccines appear to be associated with fewer mild local and systemic reactions than the "whole cell" vaccine, and few neurological events such as that alleged by the plaintiff in this case have been reported to the Japanese government's vaccine compensation system. "Acellular and Whole-Cell Pertussis Vaccines in Japan," *Journal of the American Medical Association* ("JAMA") March 13, 1987, 1351-56. Passive reporting systems such as that used in Japan, which rely on individuals to bring adverse reactions to the attention of public health authorities, are not a reliable indicator of the real incidence of adverse reactions, however.

Plaintiffs argued that various types of "non-whole cell" DPT vaccines were as effective as and safer than the "whole cell" vaccine. See Plaintiff's Trial Brief at 22. As the discussion above demonstrates, currently available scientific knowledge concerning the safety and efficacy of the new types of pertussis vaccines does not support the plaintiff's argument.

In sum, based on their evaluation of the available scientific and medical evidence, HHS's public health experts have concluded that alternative pertussis vaccines have not yet been adequately shown to be safe and effective for licensure in the United States, although studies are continuing.

4. The Federal Role.

In addition to FDA's role in the licensing and control testing of pertussis vaccines and in the conduct of research concerning the disease, the federal government is actively involved in soliciting and disseminating

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NOTES *(Continued)*

optimal size and number of doses of the acellular vaccine necessary to confer immunity, the relevance of the Japanese experience (where children are vaccinated at age two years) to the United States (where infants begin receiving pertussis immunization at age two months), and the design of laboratory tests for the vaccine that will demonstrate clinical effectiveness.

the views of outside experts on immunization policy, in directly administering federal immunization programs and assisting state programs throughout the country, and in purchasing substantial quantities of vaccine to create a federal stockpile for emergency use.

In the 1960s, the Public Health Service formed the Advisory Committee on Immunization Practices (ACIP), a body of medical specialists which is a prime source of expertise in vaccine issues. Periodically, the ACIP convenes to review vaccines and immunization practices and to make recommendations to public and private health care deliverers. Since its inception, the ACIP has consistently recommended the use of the current-licensed "whole cell" pertussis vaccine. MMWR, July 12, 1985, p.2. In reaching its recommendations, the ACIP reviewed the available data concerning the risks of the disease and the pertussis vaccine. The ACIP determined that any risks of rare, severe adverse reactions, including permanent brain damage (assuming the existence of such reactions) would be outweighed by the severe clinical course of the disease (for example, well over half of the infants with pertussis have required hospitalization), the seriousness of the possible complications and permanent consequences, and the infant fatality rate. *Id.* Specifically aware of the allegations of risks of rare, serious adverse reactions associated with the "whole cell" vaccine, the ACIP has concluded, nontheless, that vaccination against pertussis with this vaccine early in life is essential. The American Academy of Pediatrics, through its Committee on Infectious Diseases, also officially supports this conclusion regarding the importance of immunization with the "whole cell" pertussis vaccine. The Red Book, p. 266-275.

The ACIP has identified certain children who should not receive pertussis vaccine for specific medical reasons and has identified possible adverse reactions and symptoms that contraindicate further immunization with the pertussis vaccine. MMWR, July 12, 1985, p. 7.

Wyeth's physician labeling includes all warnings recommended by the ACIP.

The ACIP's recommendations appear in the *Morbidity and Mortality Weekly Report* (MMWR), the major information publication of the CDC, which is widely distributed to state and local public health officials and to physicians in private practice and academia. In addition to the publication of the ACIP's views, CDC provides technical assistance concerning immunization, including pertussis immunization, to state and local health departments through a network of regional medical epidemiologists and public health advisors. These CDC representatives are assigned to each state and to some major metropolitan areas, and they participate in their respective states' immunization programs by providing educational information, clarifying the ACIP's recommendations, and helping to ensure an adequate supply of vaccines.

CDC is also a major purchaser of DTP vaccine. In order to achieve the maximum economies of scale and thereby minimize the impact of significant recent increases in the price of the vaccine, CDC last year made a consolidated federal purchase of the vaccine for use by state public health programs.[11] This vaccine is then available at a reduced price to the state health departments for distribution in local public health clinics. The funds for this purchase are authorized under the Immunization Grant Program, formerly known as the Vaccination Assistance Act of 1962, 42 U.S.C. §247b.[12] The

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11. The CDC makes its decision from whom to purchase its DTP supply solely on the basis of cost, since CDC is convinced that the three licensed manufacturers of DTP vaccine in this country produce equally acceptable products. During the 12-month period ending in April 1987, CDC purchased nine million doses of the vaccine as part of this program.

12. Kansas receives grants under this program and is served by a CDC representative in the state who coordinates state and local programs.

CDC has developed an "Important Information Statement", based on the ACIP recommendations, which discusses the risks and benefits of the "whole cell" vaccine and which must be provided to vaccinees and/or their parents before any vaccine purchased through the federal program is administered. This statement is made freely available to state officials by CDC, and state officials then distribute the statement to their clinics and to private physicians on request. It is believed that the statement is used by many physicians in private practice to inform parents of the benefits and risks associated with immunization with the pertussis vaccine.

In addition to the consolidated federal purchase, the CDC has ordered large quantities of the vaccine in an effort to build a federal stockpile that would represent approximately a six months' supply (four million doses). The stockpiling efforts were undertaken in response to a shortage in the supply of the vaccine that occurred in 1984 when there were vaccine production problems and when two of the three licensed manufacturers stopped selling the vaccine for about six months (reportedly due to the manufacturers' inability to arrange for acceptable liability insurance coverage). The supply of DTP in 1983, which was adequate to meet the country's need, was approximately 18.2 million doses, which decreased to 15.6 million in 1984. As a result of the shortage, it was necessary for the ACIP to recommend a change in the immunization schedule, postponing the final two doses of the series of five needed for complete protection. The vaccine shortage recently experienced was a serious public health concern but its impact would appear mild in comparison with the effects of a larger and longer-lasting shortage.[13]

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13. The CDC reports that in 1986 there was another shortage of DTP vaccine in the United States. This shortfall was not as serious as that experienced in 1984, but in order to insure that all state and local health departments had an adequate amount of the vaccine, the CDC distributed between 800,000 to 900,000 doses of

While the government supports the current use of the "whole cell" vaccine, various federal public health agencies are actively involved in pertussis-related research aimed at developing new, and possibly better, types of vaccines. As mentioned above, the U.S. government was a major source of the funding for the Swedish clinical trial. Government agencies such as NIH, CDC, and FDA are also conducting studies in their own laboratories on various aspects of the disease and on new vaccines. These agencies also support research on pertussis in the private sector through grants and contracts.

The possibility that a vitally important vaccine may be denied to the public before a better alternative becomes available remains of great significance to the public health community. This concern is heightened when the current vaccine has been licensed by the FDA and when its use is strongly recommended by the Public Health Service.

NOTES *(Continued)*

the one million doses of DTP then in its stockpile. Because of this shortfall and because the manufacturers are producing the vaccine at the limit of their current capacity, it will take longer than expected to accumulate an adequate federal stockpile of the vaccine. In the opinion of the responsible agencies of the U.S. Public Health Service, the regular supply of DTP vaccine has been marginal at best for the last ten years, and a federal stockpile is therefore viewed as extremely important.

CONCLUSION

The United States presents the foregoing information to this Court.

Respectfully submitted,

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CERTIFICATE OF SERVICE

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APPENDIX E

James L. HURLEY, Jr., etc., et al., Plaintiffs-Appellants,

v.

LEDERLE LABORATORIES DIVISION OF AMERICAN CYANAMID CO., et al., Defendants-Appellees.

No. 87-2578.

United States Court of Appeals,
Fifth Circuit

Aug. 17, 1988.

As Amended on Denial of
Rehearing Jan. 5, 1989.

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Appeal from the United States District Court for the Eastern District of Texas.

Before WISDOM, REAVLEY and JOLLY, Circuit Judges.

E. GRADY JOLLY, Circuit Judge:

James Hurley III and his parents appeal the district court's partial summary judgment against their products liability claims arising from the severe neurological damage the minor Hurley sustained after innoculation

with Lederle's pertussis (whooping cough) vaccine, 651 F.Supp. 993. Since we disagree with the district court that federal law preempts the state products liability law, and since our examination of the record reveals factual questions remaining on the other issues, we reverse and remand.

I

James Hurley III was less than a year old when he was vaccinated with a DPT vaccine, which includes three separate components to immunize against diphtheria, pertussis, and tetanus. The vaccination was done with a "whole cell" pertussis component[1] manufactured by Lederle Laboratories. The child received the vaccine in the office of his personal doctor. Shortly after vaccination, the child sustained severe and irreversible neurological damage. Although Lederle included a warning in its package, this warning was never communicated to the parents. The doctor testified that the warning was adequate to apprise him of the risks inherent in the vaccine. The warning stated:

ADVERSE REACTIONS

. . . .

Neurological disorders such as encephalopathy possibly due to the pertussis component have been reported to occur rarely following the injection of this product and they may be fatal or result in permanent damage to the central nervous system.

. . . .

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1. The diphtheria and tetanus components are "toxoids": bacterial toxins artificially modified to eliminate their disease-causing potential. These virtually never cause serious adverse reactions. The pertussis component of the defendant's DPT vaccine, however, is a "whole cell" vaccine: it contains, in an inactive state, all of the components of the pertussis cell. Adverse reactions to this component are more common.

Routine immunization should be postponed or avoided in patients with acute infections or a personal or family history of neurological disturbances.

James Hurley III and his parents ("Hurley") brought this diversity action, basing their claims on the Texas law of negligence (alleging a failure to warn adequately and a failure to design the product properly), warranty (alleging breach of an express and implied warranty that the product would not injure the user in normal use), and strict products liability (alleging the production and marketing of an unreasonably dangerous product). The Hurleys maintain that the drug was unreasonably dangerous because there are alternatives to the "whole cell" pertussis vaccine currently in use in Europe and Japan. The plaintiffs contend that studies of these alternative vaccines show that they are as effective as the "whole cell" vaccine but less likely to cause the type of neurological damage sustained by their child. Although an FDA-approved vaccine similar to these alternatives was sold in the United States from 1962 to 1977, the manufacturer withdrew from the entire vaccine market and none is currently licensed by the FDA for use in the United States.

The plaintiffs also seek punitive damages under Texas law, alleging that the defendants recklessly, knowingly, and willfully failed to warn adequately of possibly severe adverse reactions to their product and to rectify the product's dangerous design.

Lederle maintains that the Hurleys' claims are preempted by federal laws that promote widespread vaccination. Lederle also argues that its warning was adequate, and that the learned intermediary doctrine applies, so that once it had warned Dr. Lanier, it had satisfied its duty.

II

The district court granted partial summary judgment in favor of the defendant, holding that federal laws, such as the Federal Food, Drug and Cosmetic Act ("FDCA"), 21 U.S.C. §310 *et seq.*, and the Public Health Service Act ("PHSA"), 42 U.S.C. §§247b and 262, and their attendant regulations, preempted any state law claims based on the inadequacy of Lederle's DPT product warning as well as any claims based on Lederle's defective design of the DPT vaccine. Moreover, the district court held under the Texas "learned intermediary" doctrine that the manufacturer had a duty to warn the prescribing physician only, rather than the patient or his parents. The district court also held that Lederle's product warning was adequate "as a matter of law" because the prescribing physician, Dr. Lanier, testified that he found it adequate. The plaintiff appeals.

III

A.

Hurley first challenges the district court's decision that federal law preempts his state law tort claims. The concept of preemption has its roots in the supremacy clause: "This Constitution, and the Laws of the United States which shall be made in Pursuance thereof . . . shall be the supreme law of the Land. . . ." United States Const. art. VI. There are basically two types of preemption, express and implied. *Hillsborough County v. Medical Laboratories, Inc.*, 471 U.S. 707, 712-14, 105 S.Ct. 2371, 2374-76, 85 L.Ed.2d 714 (1985). Lederle's argument and the district court's ruling are based on the contention that, without relief from state law products liability for the pertussis vaccine, manufacturers of the whole cell vaccine will raise prices substantially or withdraw from the market. Thus, Lederle argues and

the district court ruled, preemption of state law products liability is implied by the federal scheme to encourage vaccination.

Although the district court arrived at its holding after careful and thoughtful consideration, we must conclude that its holding is flawed. To date, the great majority of United States district courts which have addressed this issue have ruled against preemption.[2] Significantly, the judge who wrote the original opinion in *Morris v. Parke-Davis & Co.*, which found preemption,

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2. The following district court opinions have found against preemption: *Smith v. Wyeth Laboratories, Inc.*, No. CA-84-2002, slip op. (S.D. W.Va. Aug. 21, 1986); *Milam v. Lederle Laboratories Division of American Cyanamid Co.*, No. CA-4-85-92-K, slip op. (N.D.Tex. Oct. 15), 1986); *Jeski v. Connaught Laboratories, Inc.*, No. A-84-CA-395, slip op. (W.D.Tex. Dec. 18, 1986); *MacGillivray v. Lederle Laboratories Division of American Cyanamid Co.*, 667 F.Supp. 743 (N.D. N.M. 1987); *Morris v. Parke-Davis & Co.*, 667 F.Supp. 1332 (C.D.Cal. 1987); *Knudsen v. Connaught Laboratories*, 691 F.Supp. 1346 (M.D.Fla. 1987); *Martinkovic v. Wyeth Laboratories*, 669 F.Supp. 212 (N.D.Ill. 1987); *Koehler v. Wyeth Laboratories*, No. 85-284-C (S.D.Ind. Sept. 8, 1987) [1987 WL 47831]; *School v. Lederle Laboratories and Connaught Laboratories, Inc.*, No. Civ. 85-409-TUC-RMB, slip op. (D.Ariz. Nov. 25, 1987); *Percival v. American Cyanamid Co., d/b/a Lederle Laboratories*, No. Civ. 85-2671-P, slip op. (D.Okla. Nov. 25, 1987) [1987 WL 46954]; *Patten v. Lederle Laboratories*, 655 F.Supp. 745 (D.Utah 1987); *Wack v. Lederle Laboratories*, 666 F.Supp. 123 (N.D. Ohio 1987); *Graham v. Wyeth Laboratories*, 666 F.Supp. 1483 (D.Kan. 1987); *Foyle v. Lederle Laboratories*, 674 F.Supp. 530 (E.D.N.C. 1987).

Several state courts have also found no federal preemption: *Shepherd v. Lederle Laboratories*, No. 85-20330 (Cr.Ct. Broward County, Fla., Fed. 3, 1988); *Duncan v. Connaught Laboratories, Inc.*, No. 86-CVS888 (Sup.Ct. Columbus County, N.C., March 24, 1988); *Reed v. Connaught Laboratories*, 1426 Civil of 1985, (Court of Common Pleas, Monroe Co., Pa., Dec. 3, 1987).

Although the district court in *Abbott v. American Cyanamid*, No. 86-0857-A, men. op., (E.D.Va. March 1987), ruled that federal law preempted state tort remedies for DPT vaccination injuries, the Fourth Circuit recently reversed that decision, using reasoning which closely resembles our own. 844 F.2d 1108 (1988).

and upon which the district court in this case relied, subsequently withdrew and reversed his opinion to find no preemption in the light of the Supreme Court's analysis in *Hillsborough County v. Automated Medical Laboratories, Inc.*, 471 U.S. 707, 105 S.Ct. 2371, 85 L.Ed.2d 714 (1985) *Hillsborough* concerned the preemptive effects of laws of the same type as those in issue here: FDA testing and approval of medical products.

[1] As a matter of law, the district court's grounds for announcing such a rule cannot survive analysis. Although, as we shall later see, there are some instances in which state law may conflict with individual federal laws or regulations, Lederle's arguments and the district court's holding are so broadly phrased as to preempt all of state products liability law for the manufacture and distribution of the pertussis vaccine. Neither the Food, Drug and Cosmetics Act nor the Public Health Service Act *explicitly* preempts state law. Courts should be reluctant to find that federal law *implicitly* preempts state law. *Hillsborough*, 471 U.S. at 714, 105 S.Ct. at 2375. They may do so only "where the scheme of federal regulation is sufficiently comprehensive to make reasonable the inference that Congress 'left no room' for supplementary state regulation" or "where the field is one in which 'the federal interest is so dominant that the federal system will be assumed to preclude enforcement of state laws on the same subject.' " *Id.* at 713, 105 S.Ct. at 2374.[3] FDA regulation does not generally preempt stricter state law standards for medical products. *Id.* at 717-22, 105 S.Ct at 2377-80. Moreover, this and other federal courts have already ruled that FDA regulation does not preempt the types of state law duties which are

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3. Even where Congress has not completely displaced state regulations, specific state laws will be preempted (1) when simultaneous compliance with the requirements of federal and state law is impossible, or (2) when compliance with state law "stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Id.* at 713, 105 S.Ct. at 2375.

the basis of the plaintiff's claims: the duty to warn of product risks, *e.g. Osburn v. Anchor Laboratories, Inc.*, 825 F.2d 908, 911-12 (5th Cir. 1987), and the duty not to place unreasonable dangerous products into commerce. *See, e.g.*, district court cases discussed in note 2 above. It is true in theory that a policy-maker could rationally decide to relieve pertussis vaccine manufacturers of liability for product defects to ensure a reliable supply of the vaccine or to lower its cost. Nonetheless, because the absence of products liability may discourage vaccine use by increasing quality uncertainty and forcing users to bear the cost of any adverse reaction to vaccination, the ultimate effect on vaccination levels is too uncertain for a court to intrude into what is essentially a policy question. Moreover, it is not clear that the cost of compensating children injured by the vaccine would drive vaccine manufacturers from the business; the manufacturers may be able to raise prices and preserve their profit margins. Because the vaccine price is paid by the federal government, this would make the vaccination program a greater burden on the federal fisc, but it would not discourage parents from having their children vaccinated. Accordingly, the decision to preempt state law products liability would be a difficult one for a policy-maker and it is not appropriate for us to assume that decision has been made based on such inconclusive evidence.

Lederle argues that, because the FDA has not approved marketing of any alternative to the whole-cell vaccine, "the scheme of federal regulation" in this case is to encourage vaccination with the whole-cell vaccine in particular. We cannot accept this assumption because the FDA is a passive agency: it considers whether to approve vaccine designs only if and when manufacturers come forward with a proposal. *See Osburn*, 825 F.2d at 912. Thus, the absence of FDA-approved alternatives to the whole-cell vaccine does not indicate FDA disapproval of any such alternative. There is no basis for

finding a federal interest in a particular form of the pertussis vaccine.

Lederle also argues that the Public Health Services Act and its attendant regulations represent a pervasive federal scheme, and as such, preempt state law products liability for vaccine manufacturers. As Justice Marshall explains in *Hillsborough,* this argument is over inclusive:

> As a result of their specialized functions, agencies normally deal with problems in far more detail than does Congress. To infer preemption whenever an agency deals with a problem comprehensively is virtually tantamount to saying that whenever a federal agency decides to step into a field, its regulations will be exclusive.

105 S.Ct at 2377. Thus, the Supreme Court has hesitated to infer such preemption. For example, in *Silkwood v. Kerr-McGee Corp.,* 464 U.S. 238, 104 S.Ct 615, 78 L.Ed.2d 443 (1984), the Supreme Court found that the highly regulated scheme established by the Atomic Energy Act of 1954 did not implicitly preempt state tort law liability for nuclear power plant accidents. If the comprehensive and intricate plan of AEA regulation does not implicitly preempt state tort law by taking over the entire field, there is no reason to think that Congress intended the PHS vaccination program it approved in 1962, however "aggressive" it might be, to include—by implication—a holiday from state products liability law for vaccine manufacturers.

Finally, we believe that any case for preemption is doomed by the National Childhood Vaccine Injury ["NCVI"] Act of 1986, 42 U.S.C. §300aa-33. Although the NCVI Act was passed after this case was filed, it is relevant as proof that Congress intends no preemption of the state law liability of vaccine manufacturers. The NCVI Act clearly states that state law remedies apply to

the manufacture and sale of vaccines and it even makes recovery easier for injured consumers.

In sum, it is possible to construct sound policy arguments in favor of preemption in this case, but there is virtually no indication in the relevant law that Congress or the FDA explicitly or implicitly accepted them.

B.

[2] Next we consider whether the doctrine of the learned intermediary applies in this case. It is clear that this doctrine applies when a patient receives a drug or vaccination through a doctor who weighs the risks and benefits, and makes the decision to administer it. In such a case, the fact that the manufacturer has adequately warned the prescribing physician will protect it from liability to the patient for failure to warn. *Reyes v. Wyeth Laboratories,* 498 F.2d 1264 (5th Cir.1974). The doctrine becomes inapplicable, however, when vaccines are used in mass immunization programs "where no individualized medical judgment intervenes between the manufacturer . . . and the ultimate consumer . . . [In such a case,] it is the responsibility of the manufacturer to see that the warnings reach the *consumer,* either by giving the warning itself, or by obligating the purchaser to give the warning." *Id.* at 1276.

We can make several observations relating to the doctrine as it affects this case. First, the learned intermediary doctrine relates only to the issue of whom the manufacturer warned. It does not govern the adequacy of the warning. The doctrine, if it applies, will foreclose any question whether the manufacturer warned the proper party, since it is settled that the manufacturer did provide a warning in the package it sent to Dr. Lanier. Even if it does apply, however, the question may remain whether the warning adequately apprised Dr. Lanier of the risk attending the DPT vaccine. *See* Part C, *infra.* (Dr. Lanier testified that he considered the warning

adequate, but this testimony does not dispose of the question. Although his testimony is competent on the issue, the adequacy of the warning is not a matter that can be conclusively resolved solely on the basis of the administering physician's opinion.) If the learned intermediary doctrine does not apply, the general rule applies that the ultimate consumer must be warned, in this case the parents of James Hurley III.

[3] We are convinced that on the facts of this case the mass immunization exception carved out in *Reyes v. Wyeth Laboratories,* 498 F.2d 1264 (5th Cir.1974), is not applicable. Unlike *Reyes,* here the child's personal physician prescribed the shot, and the vaccine was administered under the supervision of the physician in his office by his nurse. In short, there is no question whatsoever but that a patient-physician relationship existed before and at the time the immunization was given. Indeed, Dr. Lanier testified that he had actually examined the child. Moreover, the Hurleys admitted in their complaint that the vaccine was administered under the direction and control of Dr. Lanier.

Although the Hurleys must acknowledge these basic facts, they contend that the vaccination took place in a "clinic-like" atmosphere where a nurse administered the vaccine as a routine matter and the prescribing physician did not see the patient at the time of vaccination and, in fact, was not even in his office. Furthermore, the Hurleys argue that there is no evidence before us that Dr. Lanier made an intervening professional judgment whether to administer the vaccination to James Hurley III; after all, they argue, it is this assumption of an intervening professional judgment that justifies the failure to warn the consumer directly, *see Reyes,* at 1276, and there is no basis for such an assumption here.

The Hurley's arguments, however, must be rejected in the light of our opinion in *Swayze v. McNeil Laboratories,* although the surgeon was present, he did not intervene or otherwise make any professional judgment

whether an anesthetic should be given, or in what dosage, to a patient about to undergo surgery. The patient ultimately died as a result of an overdose. Nevertheless, because the physician-patient relationship existed, and because the doctor had thus assumed the role of learned intermediary, the fact that he had made no individualized judgment did not bar the application of the learned intermediary doctrine to relieve the manufacturer of liability. We held: "Drug manufacturers must adequately warn physicians of the potential side-effects of their prescription drugs; thereafter, the physician, with his special knowledge of the patient's needs, assumes the burden of presiding over the patient's best interest." *Id.* at 472. This holding makes clear that Lederle satisfied its duty to the consumer when it warned his physician.

C.

The next question we must address concerns the adequacy of the warning Dr. Lanier received. Once again, if the district court were to decide that the learned intermediary doctrine does not apply, the question of the adequacy of this warning may ultimately be moot because it was not given to the proper party. In case the learned intermediary doctrine does apply, we turn now to consider the issues that will be before the district court on the adequacy of the warning.

[4] The defendants propose that the question of adequacy of the warning is preempted by federal law since the warning used was FDA approved. The preemption they suggest is implied preemption; in essence, they argue that state law would impermissibly conflict with federal law if it required a warning different from that approved and required by the FDA. This is the one question in this case for which the defendants' arguments on preemption are compelling; however, they are not airtight. In the area of approving warnings, although

the FDA takes an active role in designing the warning, it remains a partially passive agency. That is, it accepts information given by manufacturers proposing the licensing of a particular vaccine, and determines a proper warning based upon the information provided. 21 C.F.R. §601.2, 601.12 601.25. A state law determination on this issue should not be interjected to overrule the decision of the FDA. Such a procedure would place vaccine manufacturers in a position where they could not comply with both obligations. The FDA extensively regulates the contents and wording of these product inserts. *See, e.g.,* 21 C.F.R. §§1 and 201; 50 Fed.Reg. 51.108 (1985). A manufacturer must first provide all the relevant information to the FDA, which then determines a warning it deems appropriate. The manufacturer is required to print that precise warning in its product insert. *Id.* Most important, the manufacturers cannot change the language in the product insert without FDA approval. 21 C.F.R. §601.12. It would be patently inconsistent for a state then to hold the manufacturer liable for including that precise warning when the manufacturer would otherwise be liable for ***not*** including it. Thus, assuming that the FDA has processed all the relevant and available information in arriving at the prescribed warning, its decision as to the proper wording must preempt by implication that of a state. Specifically, such a case would fit one of the scenarios described in *KVUE, Inc. v. Austin Broadcasting Corp.* as indicating preemption: "the state statute actually and directly conflicts with federal law." 709 F.2d 922, 931-32 (5th Cir. 1983).

[5] A factual issue remains, however, as to whether the manufacturer provided the FDA all the necessary and available information on which to base the warning. Thus, the only question that can be presented to the jury consistent with the federal regulatory scheme is whether the manufacturer withheld, either at the time the FDA decided the content of the warning, or since

then, information that would have changed the FDA's decision. We believe that this issue should be presented to the jury in the form of special interrogatories, questioning whether and what information the manufacturer withheld from the FDA, if any, and whether possession of this information would have materially altered the content of the FDA's warning. This special procedure is justified by the federal interest in encouraging manufacturers to produce vaccines, in that those manufacturers need some assurance that if they follow certain prescribed procedures, such as including an FDA-approved warning, they are complying with the law.

D.

Finally, we note that the learned intermediary doctrine applies only to the inadequate warning claims; it does not address design defects. *Abbot v. American Cyanamid*, 844 F.2d 1108 (4th Cir.1988). The district court dealt with the design defect issues only under its discussion of preemption. Since we have held that preemption does not apply in this case, we must remand the design defect claims to the district court.[4]

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4. Although it would seem likely, we leave it to the district court to consider whether a parallel analysis to that applied in the warning context should apply to design-defect claims. That is, although FDA regulation has not preempted the entire field of design defect, assuming that the FDA processed all necessary and available data, does FDA approval preempt a claim that the product in design is unreasonably dangerous? We do not decide this question since we do not have the benefit of a district court's reasoning on it. We wish to make clear, however, that our holding against general preemption does not necessarily exclude the possibility of such a specific preemption.

IV

In conclusion, we hold that federal law does not preempt state products liability law governing vaccinations. We therefore remand the Hurleys' claims to the district court for further consideration. With respect to the adequacy of the warning, the record is insufficient for us to decide, since the adequacy of the warning must be determined in the light of whether Lederle withheld material information from the FDA. Otherwise, the FDA-approved warning is sufficient. Finally, the district court dealt with the remaining claims only under its preemption analysis. Since we have concluded that state product-liability law is not preempted, we remand for further proceedings not inconsistent with this opinion.

REVERSED AND REMANDED.

APPENDIX F

FOOD, DRUG, AND COSMETIC ACT, 21 U.S.C.S. § 301 et seq.

SUBCHAPTER I – SHORT TITLE

§ 301. Short title

This chapter may be cited as the Federal Food, Drug, and Cosmetic Act.

SUBCHAPTER II – DEFINITIONS

§ 321. Definitions; generally

For the purposes of this chapter –

(g) (1) The term "drug" means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clauses (A), (B), or (C) of this paragraph; but does not include devices or their components, parts, or accessories.

SUBCHAPTER III – PROHIBITED ACTS AND PENALTIES

§ 331. Prohibited acts

The following acts and the causing thereof are prohibited:

(d) The introduction or delivery for introduction into interstate commerce of any article in violation of section 344 or 355 of this title.

§333. Penalties—Violation of section 331 of this title

(a) Any person who violates a provision of section 331 of this title shall be imprisoned for not more than one year or fined not more than $1,000, or both.

§355. New drugs

(a) Necessity of effective approval of application

No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) of this section is effective with respect to such drug.

PUBLIC HEALTH SERVICE ACT, 42 U.S.C. §§201 et seq.

PART F—LICENSING OF BIOLOGICAL PRODUCTS AND CLINICAL LABORATORIES AND CONTROL OF RADIATION

Subpart I—Biological Products

§ 262. Regulation of biological products

Intrastate and interstate traffic; suspension or revocation of license as affecting prior sales

(a) No person shall sell, barter, or exchange, or offer for sale, barter, or exchange in the District of Columbia, or send, carry, or bring for sale, barter, or exchange from any State or possession into any other State or possession or into any foreign country, or from any foreign country into any State or possession, any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or its derivatives (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of diseases or injuries of man, unless (1) such virus, serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or other product has been propagated

or manufactured and prepared at an establishment holding an unsuspended and unrevoked license, issued by the Secretary as hereinafter authorized, to propagate or manufacture, and prepare such virus, serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or other product for sale in the District of Columbia, or for sending, bringing, or carrying from place to place aforesaid; and (2) each package of such virus, serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or other product is plainly marked with the proper name of the article contained therein, the name, address, and license number of the manufacturer, and the date beyond which the contents cannot be expected beyond reasonable doubt to yield their specific results. The suspension or revocation of any license shall not prevent the sale, barter, or exchange of any virus, serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or other product aforesaid which has been sold and delivered by the licensee prior to such suspension or revocation, unless the owner or custodian of such virus, serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or other product aforesaid has been notified by the Secretary not to sell, barter, or exchange the same.

Falsely labeling or marketing package or container; altering label or mark

(b) No person shall falsely label or mark any package or container of any virus, serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or other product aforesaid; nor alter any label or mark on any package or container of any virus, serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or other product aforesaid so as to falsify such label or mark.

Inspection of establishment for propagation and preparation

(c) Any officer, agent, or employee of the Department of Health and Human Services, authorized by the Secretary for the purpose, may during all reasonable hours enter and inspect any establishment for the propagation or manufacture and preparation of any virus, serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or other product aforesaid for sale, barter, or exchange in the District of Columbia, or to be sent, carried, or brought from any State or possession into any other State or possession or into any foreign country, or from any foreign country into any State or possession.

(d) Regulations governing licenses; recall of product presenting imminent hazard; violations

(1) Licenses for the maintenance of establishments for the propagation or manufacture and preparation of products described in subsection (a) of this section may be issued only upon a showing that the establishment and the products for which a license is desired meet standards, designed to insure the continued safety, purity, and potency of such products, prescribed in regulations, and licenses for new products may be issued only upon a showing that they meet such standards. All such licenses shall be issued, suspended, and revoked as prescribed by regulations and all licenses issued for the maintenance of establishments for the propagation or manufacture and preparation, in any foreign country, of any such products for sale, barter, or exchange in any State or possession shall be issued upon condition that the licensees will permit the inspection of their establishments in accordance with subsection (c) of this section.

(2)(A) Upon a determination that a batch, lot, or other quantity of a product licensed under this section presents an imminent or substantial hazard to the public

health, the Secretary shall issue an order immediately ordering the recall of such batch, lot, or other quantity of such product. An order under this paragraph shall be issued in accordance with section 554 of Title 5.

(B) Any violation of subparagraph (A) shall subject the violator to a civil penalty of up to $100,000 per day of violation. The amount of a civil penalty under this subparagraph shall, effective December 1 of each year beginning 1 year after the effective date of this subparagraph, be increased by the percent change in the Consumer Price Index for the base quarter of such year over the Consumer Price Index for the base quarter of the preceding year, adjusted to the nearest 1/10 of 1 percent. For purposes of this subparagraph, the term "base quarter", as used with respect to a year, means the calendar quarter ending on September 30 of such year and the price index for a base quarter is the arithmetical mean of such index for the 3 months comprising such quarter.

Interference with officers

(e) No person shall interfere with any officer, agent, or employee of the Service in the performance of any duty imposed upon him by this section or by regulations made by authority thereof.

Penalties for offenses

(f) Any person who shall violate, or aid or abet in violating, any of the provisions of this section shall be punished upon conviction by a fine not exceeding $500 or by imprisonment not exceeding one year, or by both such fine and imprisonment, in the discretion of the court.

Construction with other laws

(g) Nothing contained in this chapter shall be construed as in any way affecting, modifying, repealing, or

superseding the provisions of the Federal Food, Drug, and Cosmetic Act.

(h) Exportation of partially processed biological products

(1)(A) A partially processed biological product which is not in a form applicable to the prevention, treatment, or cure of diseases or injuries of man, which is not intended for sale in the United States, and which is intended for further manufacture into final dosage form outside the United States in a country listed under section 802(b)(A) of the Federal Food, Drug, and Cosmetic Act may, upon approval of an application meeting the requirements of subparagraph (B), be exported to a country listed under section 802(b)(4) of the Federal Food, Drug, and Cosmetic Act. The Secretary may not approve an application to export such a product unless the Secretary determines that the product is manufactured, processed, packaged, and held in conformity with current good manufacturing practice and the outside of the shipping package is labeled with the following statement: "This product may be sold or offered for sale only in the following countries: ",
the blank space being filled with a list of the countries to which export of the drug is authorized.

(B) An application for the export of a partially processed biological product shall—

(i) describe the partially processed biological product to be exported,

(ii) list each country to which the product is to be exported,

(iii) contain a certification by the applicant that the product will not be exported to a country not listed under clause (ii),

(iv) identify the establishments in which the product is manufactured, and

(v) contain a certification by the applicant that the final product to be developed from the partially processed product is approved in the country to which it is to be exported or approval of the final product is being sought in such country.

(2) A product described in paragraph (1) is not subject to licensure under this section.

(3) If the Secretary determines that prohibiting the export of a product described in paragraph (1) is necessary for protection of the public health in the United States or the country to which it is to be exported, the Secretary may not approve an application under paragraph (1) for the export of such product.

SUBCHAPTER XIX–VACCINES

PART 1–NATIONAL VACCINE PROGRAM

§300aa-1. Establishment

The Secretary shall establish in the Department of Health and Human Services a National Vaccine Program to achieve optimal prevention of human infectious diseases through immunization and to achieve optimal prevention against adverse reactions to vaccines. The Program shall be administered by a Director selected by the Secretary.

(July 1, 1944, c. 373, Title XXI, §2101, as added Nov. 14, 1986, Pub.L. 99-660, Title III, §311(a), 100 Stat. 3756.)

§300aa-2. Program responsibilities

(a) The Director of the Program shall have the following responsibilities:

(1) Vaccine research

The Director of the Program shall, through the plan issued under section 300aa-3 of this

title, coordinate and provide direction for research carried out in or through the National Institutes of Health, the Centers for Disease Control, the Office of Biologics Research and Review of the Food and Drug Administration, the Department of Defense, and the Agency for International Development on means to induce human immunity against naturally occurring infectious diseases and to prevent adverse reactions to vaccines.

(2) Vaccine development

The Director of the Program shall, through the plan issued under section 300aa-3 of this title, coordinate and provide direction for activities carried out in or through the National Institutes of Health, the Office of Biologics Research and Review of the Food and Drug Administration, the Department of Defense, and the Agency for International Development to develop the techniques needed to produce safe and effective vaccines.

(3) Safety and efficacy testing of vaccines

The Director of the Program shall, through the plan issued under section 300aa-3 of this title, coordinate and provide direction for safety and efficacy testing of vaccines carried out in or through the National Institutes of Health, the Centers for Disease Control, the Office of Biologics Research and Review of the Food and Drug Administration, the Department of Defense, and the Agency for International Development.

(4) Licensing of vaccine manufacturers and vaccines

The Director of the Program shall, through the plan issued under section 300aa-3 of this

title, coordinate and provide direction for the allocation of resources in the implementation of the licensing program under section 263a of this title.

(5) Production and procurement of vaccines

The Director of the Program shall, through the plan issued under section 300aa-3 of this title, ensure that the governmental and non-governmental production and procurement of safe and effective vaccines by the Public Health Service, the Department of Defense, and the Agency for International Development meet the needs of the United States population and fulfill commitments of the United States to prevent human infectious diseases in other countries.

(6) Distribution and use of vaccines

The Director of the Program shall, through the plan issued under section 300aa-3 of this title, coordinate and provide direction to the Centers for Disease Control and assistance to States, localities, and health practitioners in the distribution and use of vaccines, including efforts to encourage public acceptance of immunizations and to make health practitioners and the public aware of potential adverse reactions and contraindications to vaccines.

(7) Evaluating the need for and the effectiveness and adverse effects of vaccines and immunization activities

The Director of the Program shall, through the plan issued under section 300aa-3 of this title, coordinate and provide direction to the National Institutes of Health, the Centers for Disease Control, the Office of Biologics Re-

search and Review of the Food and Drug Administration, the National Center for Health Statistics, the National Center for Health Services Research and Health Care Technology Assessment, and the Health Care Financing Administration in monitoring the need for and the effectiveness and adverse effects of vaccines and immunization activities.

(8) Coordinating governmental and non-governmental activities

The Director of the Program shall, through the plan issued under section 300aa-3 of this title, provide for the exchange of information between Federal agencies involved in the implementation of the Program and non-governmental entities engaged in the development and production of vaccines and in vaccine research and encourage the investment of non-governmental resources complementary to the governmental activities under the Program.

(9) Funding of federal agencies

The Director of the Program shall make available to Federal agencies involved in the implementation of the plan issued under section 300aa-3 of this title funds appropriated under section 300aa-6 of this title to supplement the funds otherwise available to such agencies for activities under the plan.

(b) In carrying out subsection (a) of this section and in preparing the plan under section 300aa-3 of this title, the Director shall consult with all Federal agencies involved in research on and development, testing, licensing, production, procurement, distribution, and use of vaccines.

(July 1, 1944, c. 373, Title XXI, §2102, as added Nov. 14, 1986, Pub.L. 99-660, Title III, §311(a), 100 Stat. 3756.)

PART 2-NATIONAL VACCINE INJURY COMPENSATION PROGRAM

Subpart A—Program Requirements

§300aa-10. Establishment of program

(a) Program established

There is established the National Vaccine Injury Compensation Program to be administered by the Secretary under which compensation may be paid for a vaccine-related injury or death.

(b) Attorney's obligation

It shall be the ethical obligation of any attorney who is consulted by an individual with respect to a vaccine-related injury or death to advise such individual that compensation may be available under the program for such injury or death.

(c) Publicity

The Secretary shall undertake reasonable efforts to inform the public of the availability of the Program.

(July 1, 1944, c. 373, Title XXI, § 2110, as added Nov. 14, 1986, Pub.L. 99-660, Title III, §311(a), 100 Stat. 3758, and amended Dec. 19, 1989, Pub.L 101-239, Title VI, §6601(b), 103 Stat. 2285.)

300aa-11. Petitions for compensation

(a) General rule

(1) A proceeding for compensation under the Program for a vaccine-related injury or death shall be initiated by service upon the Secretary and the filing of a petition containing the matter prescribed by subsection (c) of this section with the United States Claims Court. The clerk of the United States Claims Court shall

immediately forward the filed petition to the chief special master for assignment to a special master under section 300aa-12(d)(1) of this title.

(2)(A) No person may bring a civil action for damages in an amount greater than $1,000 or in an unspecified amount against a vaccine administrator or manufacturer in a State or Federal court for damages arising from a vaccine-related injury or death associated with the administration of a vaccine after the effective date of this subpart, and no such court may award damages in an amount greater than $1,000 in a civil action for damages for such a vaccine-related injury or death, unless—

(i) a petition has been filed, in accordance with section 300aa-16 of this title, for compensation under the Program for such injury or death,

(ii) the United States Claims Court has issued a judgment under section 300aa-12 of this title on such petition, and

(iii) such person elects under section 300aa-21(a) of this title to file such an action.

(B) If a civil action which is barred under subparagraph (A) is filed in a State or Federal court, the court shall dismiss the action. If a petition is filed under this section with respect to the injury or death for which such civil action was brought, the date such dismissed action was filed shall, for purposes of the limitations of actions prescribed by section 300aa-16 of this title, be considered the date the petition was filed if the petition was filed within one year of the date of the dismissal of the civil action.

(3) No vaccine administrator or manufacturer may be made a party to a civil action (other than a civil action

which may be brought under paragraph (2)) for damages for a vaccine-related injury or death associated with the administration of a vaccine after the effective date of this subpart.

(4) If in a civil action brought against a vaccine administrator or manufacturer before the effective date of this subpart damages were denied for a vaccine-related injury or death or if such civil action was dismissed with prejudice, the person who brought such action may file a petition under subsection (b)) of this section for such injury or death.

(5)(A) A plaintiff who on the effective date of this subpart has pending a civil action for damages for a vaccine-related injury or death may, at any time within 2 years after the effective date of this subpart or before judgment, whichever occurs first, petition to have such action dismissed without prejudice or costs without prejudice and file a petition under subsection (b) of this section for such injury or death.

(B) If a plaintiff who has pending a civil action for damages, for a vaccine-related injury or death, such person may not file a petition under subsection (b) of this section for such injury or death.

(6) If a person brings a civil action after November 15, 1988 for damages for a vaccine-related injury or death associated with the administration of a vaccine before November 15, 1988 such person may not file a petition under subsection (b) of this section for such injury or death.

(7) If in a civil action brought against a vaccine administrator or manufacturer for a vaccine-related injury or death damages are awarded under a judgment of a court or a settlement of such action, the person who brought such action may not file a petition under subsection (b) of this section for such injury or death.

(8) If on the effective date of this subpart there was pending an appeal or rehearing with respect to a civil

action brought against a vaccine administrator or manufacturer and if the outcome of the last appellate review of such action or the last rehearing of such action is the denial of damages for a vaccine-related injury or death, the Person who brought such action may file a petition under subsection (b) of this section for such injury or death.

(9) This subsection applies only to a person who has sustained a vaccine-related injury or death and who is qualified to file a petition for compensation under the Program.

(b) Petitioners

(1)(A) Except as provided in subparagraph (B), any person who has sustained a vaccine-related injury, the legal representative of such person if such person is a minor or is disabled, or the legal representative of any person who died as the result of the administration of a vaccine set forth in the Vaccine Injury Table may, if the person meets the requirements of subsection (c)(1) of this section, file a petition for compensation under the Program.

(B) No person may file a petition for a vaccine-related injury or death associated with a vaccine administered before the effective date of this subpart if compensation has been paid under this part for 3500 petitions for such injuries or deaths.

(2) Only one petition may be filed with respect to each administration of a vaccine.

(c) Petition content

A petition for compensation under the Program for a vaccine-related injury or death shall contain—

(1) except as provided in paragraph (3), an affidavit, and supporting documentation, demonstrating that the person who suffered such injury or who died—

(A) received a vaccine set forth in the Vaccine Injury Table or, if such person did not receive such a vaccine, contracted polio, directly or indirectly, from another person who received an oral polio vaccine,

(B)(i) if such person received a vaccine set forth in the Vaccine Injury Table—

(I) received the vaccine in the United States or in its trust territories,

(II) received the vaccine outside the United States or a trust territory and at the time of the vaccination such person was a citizen of the United States serving abroad as a member of the Armed Forces or otherwise as an employee of the United States or a dependent of such a citizen, or

(III) received the vaccine outside the United States or a trust territory and the vaccine was manufactured by a vaccine manufacturer located in the United States and such person returned to the United States not later than 6 months after the date of the vaccination,

(ii) if such person did not receive such a vaccine but contracted polio from another person who received an oral polio vaccine, was a citizen of the United States or a dependent of such a citizen,

(C)(i) sustained, or had significantly aggravated, any illness, disability, injury, or condition set forth in the Vaccine Injury Table in association with the vaccine referred to in subparagraph (A) or died from the administration of

§300aa-12. Court jurisdiction

(a) General rule

The United States Claims Court and the United States Claims Court special masters shall, in accordance with this section, have jurisdiction over proceedings to determine if a petitioner under section 300aa-11 of this title is entitled to compensation under the Program and the amount of such compensation. The United States Claims Court may issue and enforce such orders as the court deems necessary to assure the prompt payment of any compensation awarded.

(b) Parties

(1) In all proceedings brought by the filing of a petition under section 300aa-11 of this title, the Secretary shall be named as the respondent, shall participate, and shall be represented in accordance with section 518(a) of Title 28.

(2) Within 30 days after the Secretary receives service of any petition filed under section 300aa-11 of this title the Secretary shall publish notice of such petition in the Federal Register. The special master designated with respect to such petition under subsection (c) of this section shall afford all interested persons an opportunity to submit relevant, written information–

(A) relating to the existence of the evidence described in section 300aa-13(a)(1)(B) of this title, or

(B) relating to any allegation in a petition with respect to the matters described in section 300aa-11(c)(1)(C)(ii) of this title.

(e) United States Claims Court special masters

(1) There is established within the United States Claims Court an office of special masters which shall

consist of not more than 8 special masters. The judges of the United States Claims Court shall appoint the special masters, 1 of whom, by designation of the judges of the United States Claims Court, shall serve as chief special master. The appointment and reappointment of the special masters shall be by the concurrence of a majority of the judges of the court.

(2) The chief special master and other special masters shall be subject to removal by the judges of the United States Claims Court for incompetency, misconduct, or neglect of duty or for physical or mental disability or for other good cause shown.

(3) A special master's office shall be terminated if the judges of the United States Claims Court determine, upon advice of the chief special master, that the services performed by that office are no longer needed.

(4) The appointment of any individual as a special master shall be for a term of 4 years, subject to termination under paragraphs (2) and (3). Individuals serving as special masters upon December 19, 1989 shall serve for 4 years from the date of their original appointment, subject to termination under paragraphs (2) and (3). The chief special master in office on December 19, 1989 shall continue to serve as chief special master for the balance of the master's term, subject to termination under paragraphs (2) and (3).

(5) The compensation of the special masters shall be determined by the judges of the United States Claims Court, upon advice of the chief special master. The salary of the chief special master shall be the annual rate of basic pay for level IV of the Executive Schedule, as prescribed by section 5315, Title 5. The salaries of the other special masters shall not exceed the annual rate of basic pay of level V of the Executive Schedule, as prescribed by section 5316, Title 5.

(6) The chief special master shall be responsible for the following:

such vaccine, and the first symptom or manifestation of the onset or of the significant aggravation of any such illness, disability, injury, or condition or the death occurred within the time period after vaccine administration set forth in the Vaccine Injury Table, or

(ii)(I) sustained, or had significantly aggravated, any illness, disability, injury, or condition not set forth in the Vaccine Injury Table but which was caused by a vaccine referred to in subparagraph (A), or

(II) sustained, or had significantly aggravated, any illness, disability, injury, or condition set forth in the Vaccine Injury Table the first symptom or manifestation of the onset or significant aggravation of which did not occur within the time period set forth in the Table but which was caused by a vaccine referred to in subparagraph (A),

(D)(i) suffered the residual effects or complications of such illness, disability, injury, or condition for more than 6 months after the administration of the vaccine and incurred unreimbursable expenses due in whole or in part to such illness, disability, injury, or condition in an amount greater than $1,000, or (ii) died from the administration of the vaccine, and

(E) has not previously collected an award or settlement of a civil action for damages for such vaccine-related injury or death,

(2) except as provided in paragraph (3) maternal prenatal and delivery records, newborn hospital records (including all physicians' and nurses' notes and test results), vaccination records associated

with the vaccine allegedly causing the injury, pre- and post-injury physician or clinic records (including all relevant growth charts and test results), all post-injury inpatient and outpatient records (including all provider notes, test results, and medication records), if applicable, a death certificate, and if applicable, autopsy results, and

(3) an identification of any records of the type described in paragraph (1) or (2) which are unavailable to the petitioner and the reasons for their unavailability.

(d) Additional information

A petition may also include other available relevant medical records relating to the person who suffered such injury or who died from the administration of the vaccine.

(e) Schedule

The petitioner shall submit in accordance with a schedule set by the special master assigned to the petition assessments, evaluations, and prognoses and such other records and documents as are reasonably necessary for the determination of the amount of compensation to be paid to, or on behalf of, the person who suffered such injury or who died from the administration of the vaccine.

(July 1, 1944, c. 373, Title XXI, §2111, as added Nov. 14, 1986, Pub.L. 99-660, Title III, §311(a), 100 Stat. 3758, and amended Dec. 22, 1987, Pub.L. 100-203, Title IV, §§4302(b), 4304(a), (b), 4306, 4307(1), (2), 101 Stat. 1330-221, 1330-223, 1330-224; Dec. 19, 1989, Pub.L. 101-239, Title VI, §660(c)(1)-(7) 103 Stat. 2285, 2286.)

(A) Administering the office of special masters and their staff, providing for the efficient, expeditious, and effective handling of petitions, and performing such other duties related to the Program as may be assigned to the chief special master by a concurrence of a majority of the United States Claims Courts judges.

(B) Appointing and fixing the salary and duties of such administrative staff as are necessary. Such staff shall be subject to removal for good cause by the chief special master.

(C) Managing and executing all aspects of budgetary and administrative affairs affecting the special masters and their staff, subject to the rules and regulations of the Judicial Conference of the United States. The Conference rules and regulations pertaining to United States magistrates shall be applied to the special masters.

(D) Coordinating with the United States Claims Court the use of services, equipment, personnel, information, and facilities of the United States Claims Court without reimbursement.

(E) Reporting annually to the Congress and the judges of the United States Claims Court on the number of petitions filed under section 300aa-11 of this title and their disposition, the dates on which the vaccine-related injuries and deaths for which the petitions were filed occurred, the types and amounts of awards, the length of time for the disposition of petitions, the cost of administering the Program, and recommendations for changes in the Program.

(d) Special masters

(1) Following the receipt and filing of a petition under section 300aa-11 of this title, the clerk of the

United States Claims Court shall forward the petition to the chief special master who shall designate a special master to carry out the functions authorized by paragraph (3).

(2) The special masters shall recommend rules to the Claims Court and, taking into account such recommended rules, the Claims Court shall promulgate rules pursuant to section 2071 of Title 28. Such rules shall—

(A) provide for a less-adversarial, expeditious, and informal proceeding for the resolution of petitions,

(B) include flexible and informal standards of admissibility of evidence,

(C) include the opportunity for summary judgment,

(D) include the opportunity for parties to submit arguments and evidence on the record without requiring routine use of oral presentations, cross examinations, or hearings, and

(E) provide for limitations on discovery and allow the special masters to replace the usual rules of discovery in civil actions in the United States Claims Court.

(3)(A) A special master to whom a petition has been assigned shall issue a decision on such petition with respect to whether compensation is to be provided under the Program and the amount of such compensation. The decision of the special master shall—

(i) include findings of fact and conclusions of law, and

(ii) be issued as expeditiously as practicable but not later than 240 days, exclusive of suspended time under subparagraph (C), after the date the petition was filed.

The decision of the special master may be reviewed by the United States Claims Court in accordance with subsection (e) of this section.

(B) In conducting a proceeding on a petition a special master—

(i) may require such evidence as may be reasonable and necessary,

(ii) may require the submission of such information as may be reasonable and necessary,

(iii) may require the testimony of any person and the production of any documents, as may be reasonable and necessary,

(iv) shall afford all interested persons an opportunity to submit relevant written information—

(I) relating to the existence of the evidence described in section 300aa-13(a)(1)(B) of this title, or

(II) relating to any allegation in a petition with respect to the matters described in section 300aa-13(c)(I)(C)(ii) of this title, and

(v) may conduct such hearings as may be reasonable and necessary.

There may be no discovery in a proceeding on a petition other than the discovery required by the special master.

(C) In conducting a proceeding on a petition a special master shall suspend the proceedings one time for 30 days on the motion of either party. After a motion for suspension is granted, further motions for suspension by either party may be granted by the special master, if the special master determines the suspension reasonable and necessary, for an aggregate period not to exceed 150 days.

(4)(A) Except as provided in subparagraph (B), information submitted to a special master or the court in

a proceeding on a petition may not be disclosed to a person who is not a party to the proceeding without the express written consent of the person who submitted the information.

(B) A decision of a special master or the court in a proceeding shall be disclosed, except that if the decision is to include information—

(i) which is trade secret or commercial or financial information which is privileged and confidential, or

(ii) which are medical files and similar files the disclosure of which would constitute a clearly unwarranted invasion of privacy,

and if the person who submitted such information objects to the inclusion of such information in the decision, the decision shall be disclosed without such information.

(e) Action by the United States Claims Court

(1) Upon issuance of the special master's decision, the parties shall have 30 days to file with the clerk of the United States Claims Court a motion to have the court review the decision. If such a motion is filed, the other party shall file a response with the clerk of the United States Claims Court no later than 30 days after the filing of such motion.

(2) Upon the filing of a motion under paragraph (1) with respect to a petition, the United States Claims Court shall have jurisdiction to undertake a review of the record of the proceedings and may thereafter—

(A) uphold the findings of fact and conclusions of law of the special master and sustain the special master's decision,

(B) set aside any findings of fact or conclusion of law of the special master found to be arbitrary,

capricious, an abuse of discretion, or otherwise not in accordance with law and issue its own findings of fact and conclusions of law, or

(C) remand the petition to the special master for further action in accordance with the court's direction.

The court shall complete its action on a petition within 120 days of the filing of a response under paragraph (1) excluding any days the petition is before a special master as a result of a remand under subparagraph (C). The court may allow not more than 90 days for remands under subparagraph (C).

(3) In the absence of a motion under paragraph (1) respecting the special master's decision or if the United States Claims Court takes the action described in paragraph (2)(A) with respect to the special master's decision, the clerk of the United States Claims Court shall immediately enter judgment in accordance with the special master's decision.

(f) Appeals

The findings of fact and conclusions of law of the United States Claims Court on a petition shall be final determinations of the matters involved, except that the Secretary or any petitioner aggrieved by the findings or conclusions of the court may obtain review of the judgment of the court in the United States court of appeals for the Federal Circuit upon petition filed within 60 days of the date of the judgment with such court of appeals within 60 days of the date of entry of the United States Claims Court's judgment with such court of appeals.

(July 1, 1944, c. 373, Title XXI, §2112, as added Nov. 14, 1986, Pub.L. 99-660, Title III, §311(a), 100 Stat. 3761; Dec. 22, 1987, Pub.L. 100-203, Title IV,

§§4303(d)(2)(A), 4307(3), 101 Stat. 1330-222, 1330-224, and amended Dec. 22, 1987, Pub.L. 100-203, Title IV, §§ 4303(d)(2)(A), 4307(3), 101 Stat, 1330-222, 1330-224, Pub.L. 100-203, Title IV, §§4307(3)(c), 4308, as amended and added July 1, 1988, Pub.L. 100-360, Title IV, §411(o)(2), (3)(A), 102 Stat. 808; Dec. 19, 1989, Pub.L. 101-239, Title VI, §6601(d)-(i) 103 Stat. 2286-2290.)

§300aa-13. Determination of eligibility and compensation

(a) General rule

(1) Compensation shall be awarded under the Program to a petitioner if the special master or court finds on the record as a whole—

(A) that the petitioner has demonstrated by a preponderance of the evidence the matters required in the petition by section 300aa-11(c)(1) of this title, and

(B) that there is not a preponderance of the evidence that the illness, disability, injury, condition, or death described in the petition is due to factors unrelated to the administration of the vaccine described in the petition.

The special master or court may not make such a finding based on the claims of a petitioner alone, unsubstantiated by medical records or by medical opinion.

(2) For purposes of paragraph (1), the term "factors unrelated to the administration of the vaccine"—

(A) does not include any idiopathic, unexplained, unknown, hypothetical, or undocumentable cause, factor, injury, illness, or condition, and

(B) may, as documented by the petitioner's evidence or other material in the record, include infection, toxins, trauma (including birth trauma

and related anoxia), or metabolic disturbances which have no known relation to the vaccine involved, but which in the particular case are shown to have been the agent or agents principally responsible for causing the petitioner's illness, disability, injury, condition, or death.

(b) Matters to be considered

(1) In determining whether to award compensation to a petitioner under the Program, the special master or court shall consider, in addition to all other relevant medical and scientific evidence contained in the record—

(A) any diagnosis, conclusion, medical judgment, or autopsy or coroner's report which is contained in the record regarding the nature, causation, and aggravation of the petitioner's illness, disability, injury, condition, or death, and

(B) the results of any diagnostic or evaluative test which are contained in the record and the summaries and conclusions.

Any such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court. In evaluating the weight to be afforded to any such diagnosis, conclusion, judgment, test result, report, or summary, the special master or court shall consider the entire record and the course of the injury, disability, illness, or condition until the date of the judgment of the special master or court.

(2) The special master or court may find the first symptom or manifestation of onset or significant aggravation of an injury, disability, illness, condition, or death described in a petition occurred within the time period described in the Vaccine Injury Table even though the occurrence of such symptom or manifestation was not recorded or was incorrectly recorded as having occurred

outside such period. Such a finding may be made only upon demonstration by a preponderance of the evidence that the onset or significant aggravation of the injury, disability, illness, condition, or death described in the petition did in fact occur within the time period described in the Vaccine Injury Table.

(c) Record defined

For purposes of this section, the term "record" means the record established by the special masters of United States Claims Court in a proceeding on a petition filed under section 300aa-11 of this title.

(July 1, 1944, c. 373, Title XXI, §2113, as added Nov. 14, 1986, Pub.L. 99-660 Title III, § 311(a), 100 Stat. 3763, and amended Dec. 22, 1987, Pub.L. 100-203, Title IV, §4307(4), 101 Stat. 1330-224. Dec. 19, 1989, Pub.L. 101-239, Title VI, §6601(j), 103 Stat. 2290.)

300aa-14. Vaccine injury table

(a) Initial table

[Table Omitted]

The following is a table of vaccines, the injuries, disabilities, illnesses, conditions, and deaths resulting from the administration of such vaccines, and the time period in which the first symptom or manifestation of onset or of the significant aggravation of such injuries, disabilities, illnesses, conditions, and deaths is to occur after vaccine administration for purposes of receiving compensation under the Program:

[Table Omitted]

(b) Qualifications and aids to interpretation

The following qualifications and aids to interpretations shall apply to the Vaccine Injury Table in subsection (a) of this section:

(1) A shock-collapse or a hypotonic-hyporesponsive collapse may be evidenced by indicia or symptoms such as decrease or loss of muscle tone, paralysis (partial or complete, hemiplegia or hemiparesis, loss of color or turning pale white or blue, unresponsiveness to environmental stimuli, depression of consciousness, loss of consciousness, prolonged sleeping with difficulty arousing, or cardiovascular or respiratory arrest.

(2) A petitioner may be considered to have suffered a residual seizure disorder if the petitioner did not suffer a seizure or convulsion unaccompanied by fever or accompanied by a fever of less than 102 degrees Fahrenheit before the first seizure or convulsion after the administration of the vaccine involved and if—

(A) in the case of a measles, mumps, or rubella vzaccine or any combination of such vaccines, the first seizure or convulsion occurred within 15 days after administration of the vaccine and 2 or more seizures or convulsions occurred within 1 year after the administration of the vaccine which were unaccompanied by fever or accompanied by a fever of less than 102 degrees Fahrenheit, and

(B) in the case of any other vaccine, the first seizure or convulsion occurred within 3 days after administration of the vaccine and 2 or more seizures or convulsions occurred within 1 year after the administration of the vaccine which were unaccompanied by fever or accompanied by a fever of less than 102 degrees Fahrenheit.

(3)(A) The term "encephalopathy" means any significant acquired abnormality of, or injury to, or impairment of function of the brain. Among the

frequent manifestations of encephalopathy are focal and diffuse neurologic signs, increased intracranial pressure, or changes lasting at least 6 hours in level of consciousness, with or without convulsions. The neurological signs and symptoms of encephalopathy may be temporary with complete recovery, or may result in various degrees of permanent impairment. Signs and symptoms such as high pitched and unusual screaming, persistent unconsolable crying, and bulging fontanel are compatible with an encephalopathy, but in and of themselves are not conclusive evidence of encephalopathy. Encephalopathy usually can be documented by slow wave activity on an electroencephalogram.

(B) If in a proceeding on a petition it is shown by a preponderance of the evidence that an encephalopathy was caused by infection, toxins, trauma, or metabolic disturbances the encephalopathy shall not be considered to be a condition set forth in the table. If at the time a judgment is entered on a petition filed under section 300aa-11 of this title for a vaccine-related injury or death it is not possible to determine the cause, by a preponderance of the evidence, of an encephalopathy, the encephalopathy shall be considered to be a condition set forth in the table. In determining whether or not an encephalopathy is a condition set forth in the table, the court shall consider the entire medical record.

(4) For purposes of paragraphs (2) and (3), the terms "seizure" and "convulsion" include grand mal, petit mal, absence, myoclonic, tonic-clonic, and focal motor seizures and signs. If a provision of the table to which paragraph (1), (2), (3), or (4) applies is revised under subsection (e) or (d) of this section, such paragraph shall not apply to such provision

after the effective date of the revision unless the revision specifies that such paragraph is to continue to apply.

(e) Administrative revision of the table

(1) The Secretary may promulgate regulations to modify in accordance with paragraph (3) the Vaccine Injury Table. In promulgating such regulations, the Secretary shall provide for notice and opportunity for a public hearing and at least 180 days of public comment.

(2) Any person (including the Advisory Commission on Childhood Vaccines) may petition the Secretary to propose regulations to amend the Vaccine Injury Table. Unless clearly frivolous, or initiated by the Commission, any such petition shall be referred to the Commission for its recommendations. Following—

(A) receipt of any recommendation of the Commission, or

(B) 180 days after the date of the referral to the Commission,

whichever occurrs first, the Secretary shall conduct a rulemaking proceeding on the matters proposed in the petition or publish in the Federal Register a statement of reasons for not conducting such proceeding.

(3) A modification of the Vaccine Injury Table under paragraph (1) may add to, or delete from, the list of injuries, disabilities, illnesses, conditions, and deaths for which compensation may be provided or may change the time periods for the first symptom or manifestation of the onset or the significant aggravation of any such injury, disability, illness, condition, or death.

(4) Any modification under paragraph (1) of the Vaccine Injury Table shall apply only with respect to petitions for compensation under the Program which are filed after the effective date of such regulation.

(d) Role of commission

Except with respect to a regulation recommended by the Advisory Commission on Childhood Vaccines, the Secretary may not propose a regulation under subsection (c) of this section or any revision thereof, unless the Secretary has first provided to the Commission a copy of the proposed regulation or revision, requested recommendations and comments by the Commission, and afforded the Commission at least 90 days to make such recommendations.

(e) Recommendation

The Secretary may recommend to Congress revisions of the table to change the vaccines covered by the table.

(July 1, 1944, c. 373, Title XXI, §2114, as added Nov. 14, 1986, Pub.L. 99-660, Title III, §311(a), 100 Stat. 3764, and amended Dec. 19, 1989, Pub.L. 101-239, Title VI, §6601(k), 103 Stat. 2290.)

300aa-15. Compensation

(a) General rule

Compensation awarded under the Program to a petitioner under section 300aa-11 of this title for a vaccine-related injury or death associated with the administration of a vaccine after the effective date of this subpart shall include the following:

(1) (A) Actual unreimbursable expenses incurred from the date of the judgment awarding such expenses and reasonable projected unreimbursable expenses which—

(i) result from the vaccine-related injury for which the petitioner seeks compensation,

(ii) have been or will be incurred by or on behalf of the person who suffered such injury, and

(iii)(I) have been or will be for diagnosis and medical or other remedial care determined to be reasonably necessary, or

(II) have been or will be for rehabilitation, developmental evaluation, special education, vocational training and placement, case management services, counseling, emotional or behavioral therapy, residential and custodial care and service expenses, special equipment, related travel expenses, and facilities determined to be reasonably necessary.

(B) Subject to section 300aa-16(a)(2) of this title, actual unreimbursable expenses incurred before the date of the judgment awarding such expenses which—

(i) resulted from the vaccine-related injury for which the petitioner seeks compensation,

(ii) were incurred by or on behalf of the person who suffered such injury, and

(iii) were for diagnosis, medical or other remedial care, rehabilitation, developmental evaluation, special education, vocational training and placement, case management services, counseling, emotional or behavioral therapy, residential and custodial care and service expenses, special equipment, related travel expenses, and facilities determined to be reasonably necessary.

(2) In the event of a vaccine-related death, an award of $250,000 for the estate of the deceased.

(3)(A) In the case of any person who has sustained a vaccine-related injury after attaining the age of 18 and whose earning capacity is or has been impaired by reason of such person's vaccine-related injury for which compensation is to be awarded, compensation for actual and anticipated loss of earnings determined in accordance with generally recognized actuarial principles and projections.

(B) In the case of any person who has sustained a vaccine-related injury before attaining the age of 18 and whose earning capacity is or has been impaired by reason of such person's vaccine-related injury for which compensation is to be awarded and whose vaccine-related injury is of sufficient severity to permit reasonable anticipation that such person is likely to suffer impaired earning capacity at 18 and beyond, compensation after attaining the age of 18 for loss of earnings determined on the basis of the average gross weekly earnings of workers in the private, non-farm sector, less appropriate taxes and the average cost of a health insurance policy, as determined by the Secretary.

(4) For actual and projected pain and suffering and emotional distress from the vaccine-related injury, an award not to exceed $250,000.

(b) Vaccines administered before effective date

Compensation awarded under the Program to a petitioner under section 300aa-11 of this title for a vaccine-related injury or death associated with the administration of a vaccine before the effective date of this subpart may include the compensation described in paragraphs (1)(A) and (2) of subsection (a) of this section and may also include an amount, not to exceed a combined total of $30,000, for—

(1) lost earnings (as provided in paragraph (3) of subsection (a) of this section),

(j) Authorization

For the payment of compensation under the Program to a petitioner for a vaccine-related injury or death associated with the administration of a vaccine before the effective date of this subpart there are authorized to be appropriated to the Department of Health and Human Services $80,000,000 for fiscal year 1989, $80,000,000 for fiscal year 1990, $80,000,000 for fiscal year 1991, $80,000,000 for fiscal year 1992, $80,000,000 for fiscal year 1993. Amounts appropriated under this subsection shall remain available until expended.

(July 1, 1944, c. 373, Title XXI, §2115, as added Nov. 14, 1986, Pub.L. 99-660, Title III, §311(a), 100 Stat. 3767, and amended Dec. 22, 1987, Pub.L. 100-203, Title IV, §§4302(b), 4303(a) to (c), (d)(1) (e), (g), 4307(5), (6), 101 Stat. 1330-221, 1330-222, 1330-223, 1330-225; July 1, 1988, Pub. L. 100-360, Title IV, §411(*o*)(1), 102 Stat. 808; Dec. 19, 1989, Pub.L. 101-239, Title V §6601(c)(8)(*l*), 103 Stat. 2286, 2290.)

§300aa-16. Limitations of actions

(a) General rule

In the case of—

(1) a vaccine set forth in the Vaccine Injury Table which is admininistered before the effective date of this subpart, if a vaccine-related injury or death occurred as a result of the administration of such vaccine, no petition may be filed for compensation under the Program for such injury or death after the expiration of 24 months after the effective date of this subpart,

(2) a vaccine set forth in the Vaccine Injury Table which is administered after the effective date of this subpart, if a vaccine-related injury occurred as a result of the administration of such vaccine, no

petition may be filed for compensation under the Program for such injury after the expiration of 36 months after the date of the occurrence of the first symptom or manifestation of onset or of the significant aggravation of such injury, and

(3) a vaccine set forth in the Vaccine Injury Table which is administered after the effective date of this subpart, if a death occurred as a result of the administration of such vaccine, no petition may be filed for compensation under the Program for such death after the expiration of 24 months from the date of the death and no such petition may be filed more than 48 months after the date of the occurrence of the first symptom or manifestation of onset or of the significant aggravation of the injury from which the death resulted.

(b) Effect of revised table

If at any time the Vaccine Injury Table is revised and the effect of such revision is to permit an individual who was not, before such revision, eligible to seek compensation under the Program, such person may file a petition for such compensation not later than 2 years after the effective date of the revision, except that no compensation may be provided under the Program with respect to a vaccine-related injury or death covered under the revision of the table if—

(1) the vaccine-related death occurred more than 8 years before the date of the revision of the table, or

(2) the vaccine-related injury occurred more than 8 years before the date of the revision of the table.

(c) State limitations of actions

If a petition is filed under section 300aa-11 of this title for a vaccine-related injury or death, limitations of actions under State law shall be stayed with respect to a civil action brought for such injury or death for the period beginning on the date the petition is filed and ending on the date a final judgment is entered on the petition.

(July 1, 1944, c. 373, Title XXI, §2116, as added Nov. 14, 1986, Pub.L. 99-660, Title III, §311(a), 100 Stat. 3769, and amended Dec. 22, 1987, Pub.L. 100-203, Title IV, §4302(b)(2), 101 Stat. 1330-221; Dec. 19, 1989, Pub.L. 101-239, Title VI, § 6601(m)(1), 103 Stat. 2291.)

§300aa-17. Subrogation

(a) General rule

Upon payment of compensation to any petitioner under the Program, the trust fund which has been established to provide such compensation shall be subrogated to all rights of the petitioner with respect to the vaccine-related injury or death for which compensation was paid, except that the trust fund may not recover under such rights an amount greater than the amount of compensation paid to the petitioner.

(b) Disposition of amounts recovered

Amounts recovered under subsection (a) of this section shall be collected on behalf of, and deposited in, the Vaccine Injury Compensation Trust Fund established under section 9510 of Title 26.

(July 1, 1944, c. 373, Title XXI, §2117, as added Nov. 14, 1986, Pub.L. 99-660, Title III, §311(a), 100 Stat. 3770, and amended Dec. 22, 1987, Pub.L. 100-203, Title IV, §4307(7), 101 Stat. 1330-225; Dec. 19, 1989, Pub.L. 101-239, Title VI, § 6601(m)(2), 103 Stat. 2291.)

300aa-19. Advisory Commission on Childhood Vaccines

(a) Establishment

There is established the Advisory Commission on Childhood Vaccines. The Commission shall be composed of:

(1) Nine members appointed by the Secretary as follows:

(A) Three members who are health professionals, who are not employees of the United States, and who have expertise in the health care of children, the epidemiology, etiology, and prevention of childhood diseases, and the adverse reactions associated with vaccines, of whom at least two shall be pediatricians.

(B) Three members from the general public, of whom at least two shall be legal representatives of children who have suffered a vaccine-related injury or death.

(C) Three members who are attorneys, of whom at least one shall be an attorney whose specialty includes representation of persons who have suffered a vaccine-related injury or death and of whom one shall be an attorney whose specialty includes representation of vaccine manufacturers.

(2) The Director of the National Institutes of Health, the Assistant Secretary for Health, the Director of the Centers for Disease Control, and the Commissioner of Food and Drugs (or the designees of such officials), each of whom shall be a nonvoting ex officio member.

The Secretary shall select members of the Commission within 90 days of the effective date of this subpart. The members of the Commission shall select a Chair from

among the members.

(b) Term of office

Appointed members of the Commission shall be appointed for a term of office of 3 years, except that of the members first appointed, 3 shall be appointed for a term of 1 year, 3 shall be appointed for a term of 2 years, and 3 shall he appointed for a term of 3 years, as detemined by the Secretary.

(c) Meetings

The Commission shall first meet within 60 davs aftaer all members of the Commission are appointed, and thereafter shall meet not less often than four times per year and at the call of the chair. A quorum for purposes of a meeting is 5. A decision at a meeting is to be made by a ballot of a majority of the voting members of the Commission.

(d) Compensation

Members of the Commission who are officers or employees of the Federal Government shall serve as members of the Commission without compensation in addition to that received in their regular public employment. Members of the Commission who are not officers or employees of the Federal Government shall be compensated at a rate not to exceed the daily equivalent of the rate in effect for grade GS-18 of the General Schedule for each day (including traveltime) they are engaged in the performance of their duties as members of the Commission. All members, while so serving away from their homes or regular places of business, may be allowed travel expenses, including per diem in lieu of subsistence, in the same manner as such expenses are authorized by section 5703, Title 5, for employees serving intermittently.

(e) Staff

The Secretary shall provide the Commission with such professional and clerical staff, such information, and the services of such consultants as may be necessary to assist the Commission in carrying out effectively its functions under this section.

(f) Functions

The Commission shall—

(1) advise the Secretary on the implementation of the Program,

(2) on its own initiative or as the result of the filing of a petition, recommend changes in the Vaccine Injury Table,

(3) advise the Secretary in implementing the Secretary's responsibilities under section 300aa-27 of this title regarding the need for childhood vaccination products that result in fewer or no significant adverse reactions,

(4) survey Federal, State, and local programs and activities relating to the gathering of information on injuries asscciated with the administration of childhood vaccines, including the adverse reaction reporting requirements of section 300aa-25(b) of this title, and advise the Secretary on means to obtain, compile, publish, and use credible data related to the frequency and severity of adverse reactions associated with childhood vaccines, and

(5) recommend to the Director of the National Vaccine Program research related to vaccine injuries which should be conducted to carry out this part.

(July 1, 1944, c. 373, Title XXI, §2119, as added Nov. 14, 1986, Pub.L. 99-660, Title III, §311(a), 100 Stat. 3771,

(2) pain and suffering (as provided in paragraph (4) of subsection (a) of this section), and

(3) reasonable attorneys' fees and costs (as provided in subsection (e) of this section).

(c) Residential and custodial care and service

The amount of any compensation for residential and custodial care and service expenses under subsection (a)(1) of this section shall be sufficient to enable the compensated person to remain living at home.

(d) Types of compensation prohibited

Compensation awarded under the Program may not include the following:

(1) Punitive or exemplary damages.

(2) Except with respect to compensation payments under paragraphs (2) and (3) of subsection (a) of this section, compensation for other than the health, education, or welfare of the person who suffered the vaccine-related injury with respect to which the compensation is paid.

(e) Attorneys' fees

(1) In awarding compensation on a petition filed under section 300aa-11 of this title the special master or court shall also award as part of such compensation an amount to cover—

(A) reasonable attorneys' fees, and

(B) other costs,

incurred in any proceeding on such petition. If the judgment of the United States Claims Court on such a petition does not award compensation, the special master or court may award an amount of compensation to cover petitioner's reasonable attorneys' fees and other

costs incurred in any proceeding on such petition if the special master or court determines that the petition was brought in good faith and there was a reasonable basis for the claim for which the petition was brought.

(2) If the petitioner, before the effective date of this subpart, filed a civil action for damages for any vaccine-related injury or death for which compensation may be awarded under the Program, and petitioned under section 300aa-11(a)(5) of this title to have such action dismissed and to file a petition for compensation under the Program, in awarding compensation on such petition the special master or court may include an amount limited to the costs and expenses incurred by the petitioner and the attorney of the petitioner before the effective date of this subpart in preparing, filing and prosecuting such civil action (including the reasonable value of the attorney's time if the civil action was filed under contingent fee arrangements).

(3) No attorney may charge any fee for services in connection with a petition filed under section 300aa-11 of this title which is in addition to an amount awarded as compensation by the special master or court under paragraph (1).

(f) Payment of compensation

(1) Except as provided in paragraph (2), no compensation may be paid until an election has been made, or has been deemed to have been made, under section 300aa-21(a) of this title to receive compensation.

(2) Compensation described in subsection (a)(1)(A)(iii) of this section shall be paid from the date of the judgment of the United States Claims Court under section 300aa-12 of this title awarding the compensation. Such compensation may not be paid after an election under section 300aa-21(b) of this title to file a civil action for damages for the vaccine-related injury or death for which such compensation was awarded.

(3) Payments of compensation under the Program and the costs of carrying out the Program shall be exempt from reduction under any order issued under part C of the Balanced Budget and Emergency Deficit Control Act of 1985 [2 U.S.C.A. §901 et seq.].

(4)(A) Except as provided in subparagraph (B), payment of compensation under the Program shall be determined on the basis of the net present value of the elements of the compensation and shall be paid from the trust fund in a lump sum of which all or a portion of the proceeds may be used as ordered by the special master to purchase an annuity or otherwise be used, with the consent of the petitioner, in a manner determined by the special master to be in the best interests, of the petitioner.

(B) In the case of a payment of compensation under the Program to a petitioner for a vaccine-related injury or death associated with the administration of a vaccine before the effective date if this subpart the compensation shall be determined on the basis of the net present value of the elements of compensation and paid in 4 equal annual installments of which all or a portion of the proceeds may be used as ordered by the special master to purchase an annuity, or otherwise be used, with the consent of the petitioner, in a manner determined by the special master to be in the best interest of the petitioner. Any reasonable attorneys' fees and costs shall be paid in a lump sum. If the appropriations under subsection (i) of this section are insufficient to make a payment of an annual installment, section 300aa-11(a) of this title shall not apply to a civil action for damages brought by the petitioner entitled to the payment.

(g) Program not primarily liable

Payment of compensation under the Program shall not be made for any item or service to the extent that payment has been made, or can reasonally be expected

to be made, with respect to such item or service (1) under any State compensation program, under an insurance policy, or under any Federal or State health benefits program (other than under title XIX of the Social Security Act [42 U.S.C.A. §1396 et seq.]), or (2) by an entity which provides health services on a prepaid basis.

(h) Liability of health insurance carrier, prepaid health plans, and benefit providers

No policy of health insurance may make payment of benefits under the policy secondary to the payment of compensation under the Program and—

(1) no State, and

(2) no entity which provides health services on a prepaid basis or provides health benefits,

may make the provision of health services or health benefits secondary to the payment of compensation under the Program, except that this subsection shall not apply to the provision of services or benefits under title XIX of the Social Security Act [42 U.S.C.A. § 1396 et seq.]).

(i) Source of compensation

(1) Payment of compensation under the Program to a petitioner for a vaccine-related injury or death associated with the administration of a vaccine before the effective date of this subpart shall be made by the Secretary from appropriations under subsection (j) of this section.

(2) Payment of compensation under the Program to a petitioner for a vaccine-related injury or death associated with the administration of a vaccine on or after the effective date of this subpart shall be made from the Vaccine Injury Compensation Trust Fund established under section 9510 of Title 26.

300aa-22. Standards of responsibility

(a) General rule

Except as provided in subsections (b), (c), and (e) of this section State law shall apply to a civil action brought for damages for a vaccine-related injury or death.

(b) Unavoidable adverse side effects; warnings

(1) No vaccine manufacturer shall be liable in a civil action for damages arising from a vaccine-related injury or death associated with the administration of a vaccine after the effective date of this subpart if the injury or death resulted from side effects that were unavoidable even though the vaccine was properly prepared and was accompanied by proper directions and warnings.

(2) For purposes of paragraph (1), a vaccine shall be presumed to be accompanied by proper directions and warnings if the vaccine manufacturer shows that it complied in all material respects with all requirements under the Federal Food, Drug, and Cosmetic Act [21 U.S.C.A. §301 et seq.] and section 262 of this title (including regulations issued under such provisions) applicable to the vaccine and related to vaccine-related injury or death for which the civil action was brought unless the plaintiff shows—

(A) that the manufacturer engaged in the conduct set forth in subparagraph (A) or (B) of section 300aa-23(d)(2) of this title, or

(B) by clear and convincing evidence that the manufacturer failed to exercise due care notwithstanding its compliance with such Act and section (and regulations issued under such provisions).

(c) Direct warnings

No vaccine manufacturer shall be liable in a civil action for damages arising from a vaccine-related injury

or death associated with the administration of a vaccine after the effective date of this subpart solely due to the manufacturer's failure to provide direct warnings to the injured party (or the injured party's legal representative) of the potential dangers resulting from the administration of the vaccine manufactured by the manufacturer.

(d) Construction

The standards of responsibility prescribed bv this section are not to be construed as authorizing a person who brought a civil action for damages against a vaccine manufacturer for a vaccine-related injury or death in which damages were denied or which was dismissed with prejudice to bring a new civil action against such manufacturer for such injury or death.

(e) Preemption

No State may establish or enforce a law which prohibit an individual from bringing a civil action against a vaccine manufacturer for damages for a vaccine-related injury or death if such civil action is not barred by this part.

(July 1, 1944, c. 373, Title XXI, §2122, as added Nov. 14, Pub.L. 99-660, Title III, §311(a), 100 Stat. 3773, and amended Dec. 22, 1987, Pub.L. 100-203, Title IV, §4302(b)(1), 101 Stat. 1330-221.)

300aa-23. Trial

(a) General rule

A civil action against a vaccine manufacturer for damages for a vaccine-related injury or death associated with the administration of a vaccine after the effective date of this subpart which is not barred by section 300aa-11 (a)(2) of this title shall be tried in three stages.

and amended Dec. 22, 1987, Pub.L. 100-203, Title IV, §4302(b)(1), 101 Stat. 1330-221.)

Subpart B—Additional Remedies

300aa-21. Authority to bring actions

(a) Election

After judgment has been entered by the United States Claims Court or, if an appeal is taken under section 300aa-12(f) of this title, after the appellate, court's mandate is issued, the petitioner who filed the petition under section 300aa-11 of this title shall file with the clerk of the United States Claims Court—

(1) if the judgment awarded compensation, an election in writing to receive the compensation or to file a civil action for damages for such injury or death, or

(2) if the judgment did not award compensation, an election in writing to accept the judgment or to file a civil action for damages for such injury or death.

An election shall be filed under this subsection not later than 90 days after the date of the court's final judgment with respect to which the election is to be made. If a person required to file an election with the court under this subsection does not file the election within the time prescribed for filing the election, such person shall be deemed to have filed an election to accept the judgment of the court. For limitations on the bringing of civil actions, see section 300aa-11(a)(2) of this title.

(b) Withdrawal of petition

If the United States Claim Court fails to enter a judgment under section 300aa-12 of this title on a petition filed under section 300aa-11 of this title within

420 days (excluding any period of suspension under section 300aa-11(d) of this title and excluding any days the petition is before a special master as a result of a remand under section 300aa-11(e)(2)(C) of this title) after the date on which the petition was filed, the petitioner may submit to the court a notice in writing withdrawing the petition. An election shall be filed under this subsection not later than 90 days after the date of the entry of the Claims Court's judgment or the appellate court's mandate with respect to which the election is to be made. A person who has submitted a notice under this subsection may, notwithstanding section 300aa-11(a)(2) of this title, thereafter maintain a civil action for damages in a State or Federal court without regard to subpart B of this part and consistent with otherwise applicable law.

(c) Limitations of actions

A civil action for damages arising from a vaccine-related injury or death for which a petition was filed under section 300aa-11 of this title shall, except as provided in section 300aa-16(b) of this title, be brought within the period prescribed by limitations of actions under State law applicable to such civil action.

(July 1, 1944, c. 373, Title XXI, §2121, as added Nov. 14, 1986, Pub.L. 99-660, Title III, §311(a), 100 Stat. 3772, and amended Dec. 22, 1987, Pub.L. 100-203, Title IV, §§4304(c), 4307(8), 101 Stat. 1330-224, 1330-225; July 1, 1988, Pub.L. 100-360, Title IV, §411*(o)*(3)(A), 102 Stat. 808; Dec. 19, 1989, Pub.L. 101-239, Title VI, §6601(n), 103 Stat. 2292.)

(b) Liability

The first stage of such a civil action shall be held to determine if a vaccine manufacturer is liable under section 300aa-22 of this title.

(c) General damages

The second stage of such a civil action shall be held to determine the amount of damages (other than punitive damages) a vaccine manufacturer found to be liable under section 300aa-22 of this title shall be required to pay.

(d) Punitive damages

(1) If sought by the plaintiff, the third stage of such an action shall be held to determine the amount of punitive damages a vaccine manufacturer found to be liable under section 300aa-22 of this title shall be required to pay.

(2) If in such an action the manufacturer shows that it complied, in all material respects, with all requirements under the Federal Food, Drug, and Cosmetic Act [21 U.S.C.A. §301 et seq.] and this chapter applicable to the vaccine and related to the vaccine injury or death with respect to which the action was brought, the manufacturer shall not he held liable for punitive damages unless the manufacturer engaged in—

(A) fraud or intentional and wrongful withholding of information from the Secretary during any phase of a proceeding for approval of the vaccine under section 262 of this title,

(B) intentional and wrongful withholding of information relating to the safety or efficacy of the vaccine after its approval, or

(C) other criminal or illegal activity relating to the safety and effectiveness of vaccines,

which activity related to the vaccine-related injury or death for which the civil action was brought.

(e) Evidence

In any stage of a civil action, the Vaccine Injury Table, any finding of fact or conclusion of law of the United States Claims Court or a special master in a proceeding on a petition filed under section 300aa-11 of the title and the final judgment of the United States Claims Court and subsequent appellate review on such a petition shall not be admissible.

21 C.F.R. (1979)

SUBCHAPTER F – BIOLOGICS

PART 600 – BIOLOGICAL PRODUCTS: GENERAL

Subpart A – General Provisions

Sec.

600.3 Definitions.

Subpart B – Establishment Standards

600.10 Personnel.
600.11 Physical establishment, equipment, animals, and care.
600.12 Records.
600.13 Retention samples.
600.14 Reporting of errors.
600.15 Temperatures during shipment.

Subpart C – Establishment Inspection

600.20 Inspectors.
600.21 Time of inspection.
600.22 Duties of inspector.

Subpart A—General Provisions

§600.3 Definitions.

As used in this subchapter:

(a) "Act" means the Public Health Service Act (58 Stat. 682), approved July 1, 1944.

(b) "Secretary" means the Secretary of Health, Education, and Welfare and any other officer or employee of the Department of Health, Education, and Welfare to whom the authority involved has been delegated.

(c) "Commissioner of Food and Drugs" means the Commissioner of the Food and Drug Administration.

(d) "Bureau of Biologics" means the Bureau of Biologics of the Food and Drug Administration.

(e) "State" means a State or the District of Columbia, Puerto Rico, or the Virgin Islands.

(f) "Possession" includes among other possessions, Puerto Rico and the Virgin Islands.

(g) "Products" includes biological products and trivalent organic arsenicals.

(h) "Biological product" means any virus, therapeutic serum, toxin, anti-toxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man:

(1) A virus is interpreted to be a product containing the minute living cause of an infectious disease and includes but is not limited to filterable viruses, bacteria, rickettsia, fungi, and protozoa.

(2) A therapeutic serum is a product obtained from blood by removing the clot or clot components and the blood cells.

(3) A toxin is a product containing a soluble substance poisonous to laboratory animals or to man in doses of 1 milliliter or less (or equivalent in weight) of the product, and having the property, following the injection of non-fatal doses into an animal, of causing to be produced therein another soluble substance which

specifically neutralizes the poisonous substance and which is demonstrable in the serum of the animal thus immunized.

(4) An antitoxin is a product containing the soluble substance in serum or other body fluid of an immunized animal which specifically neutralizes the toxin against which the animal is immune.

(5) A product is analogous:

(i) To a virus if prepared from or with a virus or agent actually or potentially infectious, without regard to the degree of virulence or toxicogenicity of the specific strain used.

(ii) To a therapeutic serum, if composed of whole blood or plasma or containing some organic constituent or product other than a hormone or an amino acid, derived from whole blood, plasma, or serum.

§600.11 Physical establishment, equipment, animals, and care.

(a) *Work areas.* All rooms and work areas where products are manufactured or stored shall be kept orderly, clean, and free of dirt, dust, vermin and objects not required for manufacturing. Precautions shall be taken to avoid clogging and back-siphonage of drainage systems. Precautions shall be taken to exclude extraneous infectious agents from manufacturing areas. Work rooms shall be well lighted and ventilated. The ventilation system shall be arranged so as to prevent the dissemination of microorganisms from one manufacturing area to another and to avoid other conditions unfavorable to the safety of the product. Filling rooms, and other rooms where open, sterile operations are conducted, shall be adequate to meet manufacturing needs and such rooms shall be constructed and equipped to permit thorough cleaning and to keep air-borne contaminants at a minimum. If such rooms are used for other purposes, they shall be cleaned and prepared prior to use

for sterile operations. Refrigerators, incubators and warm rooms shall be maintained at temperatures within applicable ranges and shall be free of extraneous material which might affect the safety of the product.

(b) *Equipment.* Apparatus for sterilizing equipment and the method of operation shall be such as to insure the destruction of contaminating microorganisms. The effectiveness of the sterilization procedure shall be no less than that achieved by an attained temperature of 121.5° C maintained for 20 minutes by saturated steam or by an attained temperature of 170° C maintained for 2 hours with dry heat. Processing and storage containers, filters, filling apparatus, and other pieces of apparatus and accessory equipment, including pipes and tubing, shall be designed and constructed to permit thorough cleaning and, where possible, inspection for cleanliness. All surfaces that come in contact with products shall be clean and free of surface solids, leachable contaminants, and other materials that will hasten the deterioration of the product or otherwise render it less suitable for the intended use. For products for which sterility is a factor, equipment shall be sterile, unless sterility of the product is assured by subsequent procedures.

(c) *Laboratory and bleeding rooms.* Rooms used for the processing of products, including bleeding rooms, shall be effectively fly-proofed and kept free of flies and vermin. Such rooms shall be so constructed as to insure freedom from dust, smoke and other deleterious substances and to permit thorough cleaning and disinfection. Rooms for animal injection and bleeding, and rooms for smallpox vaccine animals, shall be disinfected and be provided with the necessary water, electrical and other services.

(d) *Animal quarters and stables.* Animal quarters, stables and food storage areas shall be of appropriate

construction, fly-proofed, adequately lighted and ventilated, and maintained in a clean, vermin-free and sanitary condition. No manure or refuse shall be stored as to permit the breeding of flies on the premises, nor shall the establishment be located in close proximity to off-property manure or refuse storage capable of engendering fly breeding.

(e) *Restrictions on building and equipment use*— (1) Work of a diagnostic nature. Laboratory procedures of a clinical diagnostic nature involving materials that may be contaminated, shall not be performed in space used for the manufacture of products except that manufacturing space which is used only occasionally may be used for diagnostic work provided spore-bearing pathogenic microorganisms are not involved and provided the space is thoroughly cleaned and disinfected before the manufacture of products is resumed.

(2) *Spore-bearing organisms for supplemental sterilization procedure control test.* Spore-bearing organisms used as an additional control in sterilization procedures may be introduced into areas used for the manufacture of products, only for the purposes of the test and only immediately before use for such purposes: *Provided,* That (i) the organism is not pathogenic for man or animals and does not produce pyrogens or toxins, (ii) the culture is demonstrated to be pure, (iii) transfer of test cultures to culture media shall be limited to the sterility test area or areas designated for work with spore-bearing organisms, (iv) each culture be labeled with the name of the microorganism and the statement "Caution: microbial spores. See directions for storage, use and disposition.", and (v) the container of each culture is designed to withstand handling without breaking.

(3) *Work with spore-bearing organisms.* Except as provided in the previous paragraph, all work with spore-bearing microorganisms shall be done in an entirely separate building: *Provided,* That such work may

be done in a portion of a building used in the manufacture of products not containing spore-bearing microorganisms if such portion is completely walled-off and is constructed so as to prevent contamination of other areas and if entrances to such portion are independent of the remainder of the building. All vessels, apparatus and equipment used for spore-bearing microorganisms shall be permanently identified and reserved exclusively for use with those organisms. Materials destined for further manufacturing may be removed from such an area only under conditions which will prevent the introduction of spores into other manufacturing areas.

(4) *Live vaccine processing.* Space used for processing a live vaccine shall not be used for any other purpose during the processing period for that vaccine and such space shall be decontaminated prior to initiation of the processing. Live vaccine processing areas shall be isolated from and independent of any space used for any other purpose by being either in a separate building, in a separate wing of a building, or in quarters at the blind end of a corridor and shall include adequate space and equipment for all processing steps up to filling into final containers. Test procedures which potentially involve the presence of microorganisms other than the vaccine strains, or the use of tissue culture cell lines other than primary cultures, shall not be conducted in space used for processing live vaccine.

(5) *Equipment and supplies—contamination.* Equipment and supplies used in work on or otherwise exposed to any pathogenic or potentially pathogenic agent shall be kept separated from equipment and supplies used in the manufacture of products to the extent necessary to prevent cross-contamination.

(f) *Animals used in manufacture*—(1) *Care of animals used in manufacturing.* Caretakers and attendants for animals used for the manufacture of products shall be sufficient in number and have adequate experience to insure adequate care. Animal quarters and

cages shall be kept in sanitary condition. Animals on production shall be inspected daily to observe response to production procedures. Animals that become ill for reasons not related to production shall be isolated from other animals and shall not be used for production until recovery is complete. Competent veterinary care shall be provided as needed.

(2) *Quarantine of animals*—(i) *General.* No animal shall be used in processing unless kept under competent daily inspection and preliminary quarantine for a period of at least 7 days before use, or as otherwise provided in this subchapter. Only healthy animals free from detectable communicable diseases shall be used. Animals must remain in overt good health throughout the quarantine periods and particular care shall be taken during the quarantine periods to reject animals of the equine genus which may be infected with glanders and animals which may be infected with tuberculosis.

(ii) *Quarantine of monkeys.* In addition to observing the pertinent general quarantine requirements, monkeys used as a source of tissue in the manufacture of vaccine shall be maintained in quarantine for at least 6 weeks prior to use, except when otherwise provided in this part. Only monkeys that have reacted negatively to tuberculin at the start of the quarantine period and again within 2 weeks prior to use shall be used in the manufacture of vaccine. Due precaution shall be taken to prevent cross-infection from any infected or potentially infected monkeys on the premises. Monkeys to be used in the manufacture of a live vaccine shall be maintained throughout the quarantine period in cages closed on all sides with solid materials except the front which shall be screened, with no more than two monkeys housed in one cage. Cage mates shall not be interchanged.

(3) *Immunization against tetanus.* Horses and other animals susceptible to tetanus, that are used in the

processing steps of the manufacture of biological products, shall be treated adequately to maintain immunity to tetanus.

(4) *Immunization and bleeding of animals used as a source of products.* Toxins or other nonviable antigens administered in the immunization of animals used in the manufacture of products shall be sterile. Viable antigens, when so used, shall be free of contaminants, as determined by appropriate tests prior to use. Injections shall not be made into horses within 6 inches of bleeding site. Horses shall not be bled for manufacturing purposes while showing persistent general reaction or local reaction near the site of bleeding. Blood shall not be used if it was drawn within 5 days of injecting the animals with viable microorganisms. Animals shall not be bled for manufacturing purposes when they have an intercurrent disease. Blood intended for use as a source of a biological product shall be collected in clean, sterile vessels. When the product is intended for use by injection, such vessels shall also be pyrogen-free.

(5) [Reserved]

(6) *Reporting of certain diseases.* In cases of actual or suspected infection with foot and mouth disease, glanders, tetanus, anthrax, gas gangrene, equine infectious anemia; equine encephalomyelitis, or any of the pock diseases among animals intended for use or used in the manufacture of products, the manufacturer shall immediately notify the Director, Bureau of Biologics.

(7) *Monkeys used previously for experimental or test purposes.* Monkeys that have been used previously for experimental or test purposes with live microbiological agents shall not be used as a source of kidney tissue for the manufacture of vaccine. Except as provided otherwise in this subchapter, monkeys that have been used previously for other experimental or test purposes may be used as a source of kidney tissue upon their return to a normal condition, provided all quarantine requirements have been met.

(8) *Necropsy examination of monkeys.* Each monkey used in the manufacture of vaccine shall be examined at necropsy under the direction of a qualified pathologist, physician, or veterinarian having experience with diseases of monkeys, for evidence of ill health, particularly for (i) evidence of tuberculosis, (ii) presence of herpes-like lesions, including eruptions or plaques on or around the lips, in the buccal cavity or on the gums, and (iii) signs of conjunctivitis. If there are any such signs or other significant gross pathological lesions, the tissue shall not be used in the manufacture of vaccine.

(g) *Filling procedures.* Filling procedures shall be such as will not affect adversely the safety, purity or potency of the product.

(h) *Containers and closures.* All final containers and closures shall be made of material that will not hasten the deterioration of the product or otherwise render it less suitable for the intended use. All final containers and closures shall be clean and free of surface solids, leachable contaminants and other materials that will hasten the deterioration of the product or otherwise render it less suitable for the intended use. After filling, sealing shall be performed in a manner that will maintain the integrity of the product during the dating period. In addition, final containers and closures for products intended for use by injection shall be sterile and free from pyrogens. Except as otherwise provided in the regulations of this subchapter, final containers for products intended for use by injection shall be colorless and sufficiently transparent to permit visual examination of the contents under normal light. As soon as possible after filling final containers shall be labeled as prescribed in §610.60 et seq. of this chapter, except that final containers may be stored without such prescribed labeling provided they are stored in a sealed receptacle labeled both inside and outside with at least the name of the product, the lot number, and the filling identification.

[38 FR 32048, Nov. 20, 1973, as amended at 41 FR 10428, Mar. 11, 1976]

§600.12 Records.

(a) *Maintenance of records.* Records shall be made, concurrently with the performance, of each step in the manufacture and distribution of products, in such a manner that at any time successive steps in the manufacture and distribution of any lot may be traced by an inspector. Such records shall be legible and indelible, shall identify the person immediately responsible, shall include dates of the various steps, and be as detailed as necessary for clear understanding of each step by one experienced in the manufacture of products.

(b) *Records retention*—(1) *General.* Records shall be retained for such interval beyond the expiration date as is necessary for the individual product, to permit the return of any clinical report of unfavorable reactions. The retention period shall be no less than five years after the records of manufacture have been completed or six months after the latest expiration date for the individual product, whichever represents a later date.

(2) *Records of recall.* Complete records shall be maintained pertaining to the recall from distribution of any product upon notification by the Director, Bureau of Biologics, to recall for failure to conform with the standards prescribed in the regulations of this subchapter, because of deterioration of the product or for any other factor by reason of which the distribution of the product would constitute a danger to health.

(3) *Suspension of requirement for retention.* The Director, Bureau of Biologics, may authorize the suspension of the requirement to retain records of a specific manufacturing step upon a showing that such records no longer have significance for the purposes for which they were made: *Provided,* That a summary of such records shall be retained.

(c) *Records of sterilization of equipment and supplies.* Records relating to the mode of sterilization, date, duration, temperature and other conditions relating to each sterilization of equipment and supplies used in the processing of products shall be made by means of automatic recording devices or by means of a system of recording which gives equivalent assurance of the accuracy and reliability of the record. Such records shall be maintained in a manner that permits an identification of the product with the particular manufacturing process to which the sterilization relates.

(d) *Animal necropsy records.* A necropsy record shall be kept on each animal from which a biological product has been obtained and which dies or is sacrificed while being so used.

(e) *Records in case of divided manufacturing responsibility.* If two or more establishments participate in the manufacture of a product, the records of each such establishment must show plainly the degree of its responsibility. In addition, each participating manufacturer shall furnish to the manufacturer who prepares the product in final form for sale, barter or exchange, a copy of all records relating to the manufacturing operations performed by such participating manufacturer insofar as they concern the safety, purity and potency of the lots of the product involved, and the manufacturer who prepares the product in final form shall retain a complete record of all the manufacturing operations relating to the product.

§600.13 Retention samples.

Manufacturers shall retain for a period of at least 6 months after the expiration date, unless a different time period is specified in additional standards, a quantity of representative material of each lot of each product, sufficient for examination and testing for safety and

potency, except Whole Blood (Human), Cryoprecipitated Antihemophilic Factor (Human), Platelet Concentrate (Human), Red Blood Cells (Human), Single Donor Plasma (Human), Source Plasma (Human), and Allergenic Products prepared to physician's prescription. Samples so retained shall be selected at random from either final container material, or from bulk and final containers, provided they include at least one final container as a final package, or package-equivalent of such filling of each lot of the product as intended for distribution. Such sample material shall be stored at temperatures and under conditions which will maintain the identity and integrity of the product. Samples remained as required in this section shall be in addition to samples of specific products required to be submitted to the Bureau of Biologics. Exceptions may be authorized by the Director, Bureau of Biologics, when the lot yields relatively few final containers and when such lots are prepared by the same method in large number and in close succession.

[41 FR 10428, Mar. 11, 1976]

§600.14 Reporting of errors.

The Director, Bureau of Biologics, shall be notified promptly of errors or accidents in the manufacture of products that may affect the safety, purity, or potency of any product.

§600.15 Temperatures during shipment.

The following products shall be maintained during shipment at the specified temperatures:

(a) *Products.*

(b) *Exemptions.* Exemptions or modifications shall be made only upon written approval, in the form of an amendment of the product license, issued by the Director, Bureau of Biologics.

601.3 License forms.
601.4 Issuance and denial of license.
601.5 Revocation of license.
601.6 Suspension of license.
601.7 Procedure for hearings.
601.8 Publication of revocation.
601.9 Licenses; reissuance.

Subpart B—Establishment Licensing

601.10 Establishment licenses; issuance and conditions.
601.12 Changes to be reported.

Subpart C—Product Licensing

601.20 Product licenses; issuance and conditions.
601.21 Products under development.
601.22 Products in short supply; initial manufacturing at other than licensed establishment.
601.25 Review procedures to determine that licensed biological products are safe, effective, and not misbranded under prescribed, recommended, or suggested conditions of use.

Subpart D—Licensing of Foreign Establishments and Products

601.30 Licenses required; products for controlled investigation only.
601.31 Procedure.
601.32 Form of license.
601.33 Samples for each importation.

Subpart E—[Reserved]

Subpart F—Confidentiality of Information

601.50 Confidentiality of data and information in an investigational new drug notice for a biological product.

601.51 Confidentiality of data and information in applications for establishment and product licenses.

AUTHORITY: Sec. 215, 58 Stat. 690, as amended; 42 U.S.C. 216. Sec. 351, 58 Stat. 702, as amended; 42 U.S.C. 262, unless otherwise noted.

SOURCE: 38 FR 32052, Nov. 20, 1973, unless otherwise noted.

CROSS REFERENCES: For U.S. Customs Service regulations relating to viruses, serums, and toxins, see 19 CFR 12.21-12.23. For U.S. Postal Service regulations relating to the admissibility to the United States mails see Parts 124 and 125 of the Postal Service Manual, that is incorporated by reference in 39 CFR Part III.

Subpart A—General Provisions

§601.1 Two forms of licenses.

There shall be two forms of licenses: establishment and product.

§601.2 Applications for establishment and product licenses; procedures for filing.

(a) *General.* To obtain a license for any establishment or product, the manufacturer shall make application to the Director, Bureau of Biologics, on forms prescribed for such purposes, and in the case of an application for a product license, shall submit data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed standards of safety, purity, and potency; with respect to each nonclinical laboratory study, either a statement that the study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a statement that describes in detail all differences between the practices used in the study and those required in the regulations;

a full description of manufacturing methods; data establishing stability of the product through the dating period; sample(s) representative of the product to be sold, bartered, or exchanged or offered, sent, carried or brought for sale, barter, or exchange; summaries of results of tests performed on the lot(s) represented by the submitted sample(s); and specimens of the labels, enclosures and containers proposed to be used for the product. An application for license shall not be considered as filed until all pertinent information and data shall have been received from the manufacturer by the Bureau of Biologics. The applicant shall also include an environmental impact analysis report analyzing the environmental impact of the manufacturing process and the ultimate use or consumption of the biological product pursuant to §25.1 of this chapter. In lieu of the procedures described in this paragraph, applications for radioactive biological products shall be handled as set forth in paragraph (b) of this section.

(b) *Radioactive biological products.* In lieu of submitting an establishment and product license for the manufacture of a radioactive biological product, as defined in §600.3(ee) of this chapter, the manufacturer of such a product shall submit a new drug application to the Director, Division of Oncology and Radiopharmaceutical Drug Products, Bureau of Drugs, Food and Drug Administration, 5600 Fishers Lane, Rockville, Md. 20857, on form FD-356(H) as set forth in §314.1(c)(2) of this chapter. For such products, the approval of the new drug application will be in lieu of issuing a product and an establishment license. Compliance with the provisions of Part 314 of this chapter shall be deemed to constitute compliance with the provisions of Subchapter F of this chapter unless the Commissioner makes a determination that a particular regulation from Subchapter F shall be applicable to radioactive drugs containing a biological product, e.g., §610.2 of this chapter.

(Sec. 102(2)(C), Pub. L. 91-190, 83 Stat. 853 (42 U.S.C. 4332); secs. 406, 408, 409, 502, 503, 505, 506, 507, 510, 512-516, 518-520, 601, 701, 706, and 801, Pub. L. 717, 52 Stat. 1049-1056 as amended, 1058 as amended ; 55 Stat. 851 as amended, 59 Stat. 463 as amended, 68 Stat. 511-517, as amended, 72 Stat. 1785-1788 as amended, 76 Stat. 794, as amended, 82 Stat. 343-351, 90 Stat. 539-574 (21 U.S.C. 346, 346a, 348, 352, 353, 355, 356, 357, 360, 360b-360f, 360h-360i, 371) secs. 2 et seq., Pub. L. 89-755, 80 Stat. 1296 et seq. (15 U.S.C. 1451 et seq.); secs. 215, 301, 351, 352, 354-360F, Pub. L. 410, 58 Stat. 690, 702 as amended by 81 Stat. 536, 82 Stat. 1173 et seq. (42 U.S.C. 216, 262, 263, 263b-263n))

[40 FR 31313, July 25, 1975, as amended at 43 FR 60024, Dec. 22, 1978; 44 FR 17657, Mar. 23, 1979]

EFFECTIVE DATE NOTE: At 43 FR 60024, Dec. 22, 1978, §601.2(a) was revised, effective June 20, 1979. For the convenience of the user, the superseded text is set forth below.

§601.2 Applications for establishment and product licensees; procedure for filing.

(a) *General.* To obtain a license for any establishment or product, the manufacturer shall make application to the Director, Bureau of Biologics, on forms prescribed for such purpose, and in the case of an application for a product license, shall submit data derived from laboratory and clinical studies which demonstrate that the manufactured product meets prescribed standards of safety, purity, and potency; a full description of manufacturing methods; data establishing stability of the product through the dating period; sample(s) representative of the product to be sold, bartered, or exchanged or offered, sent, carried or brought for sale, barter, or exchange; summaries of results of tests performed on the lot(s) represented by the submitted sample(s); and specimens of the labels,

[39 FR 39872, Nov. 12, 1974, as amended at 40 FR 4304, Jan. 29, 1975; 42 FR 10983, Feb. 25, 1977; 42 FR 58677, Nov. 22, 1977]

Subpart C—Establishment Inspection

§600.20 Inspectors.

Inspections shall be made by an officer of the Food and Drug Administration having special knowledge of the methods used in the manufacture and control of products and designated for such purposes by the Commissioner of Food and Drugs, or by any officer, agent, or employee of the Department of Health, Education, and Welfare specifically designated for such purpose by the Secretary.

§600.21 Time of Inspection.

The inspection of an establishment for which a license is pending need not be made until the establishment is in operation and is manufacturing the complete product for which a product license is desired. In case the license is denied following inspection for the original license, no reinspection need be made until assurance has been received that the faulty conditions which were the basis of the denial have been corrected. An inspection of each licensed establishment shall be made at least once each year. Inspections may be made with or without notice, and shall be made during regular business hours unless otherwise directed.

§600.22 Duties of Inspector.

The inspector shall:

(a) Call upon the active head of the establishment, stating the object of his visit.

(b) Interrogate the proprietor or other personnel of the establishment as he may deem necessary.

(c) Examine the details of location, construction, equipment and maintenance, including stables, barns, warehouses, manufacturing laboratories, bleeding clinics maintained for the collection of human blood, shipping rooms, record rooms, and any other structure or appliance used in any part of the manufacture of a product.

(d) Investigate as fully as he deems necessary the methods of propagation, processing, testing, storing, dispensing, recording, or other details of manufacture and distribution of each licensed product, or product for which a license has been requested, including observation of these procedures in actual operation.

(e) Obtain and cause to be sent to the Director, Bureau of Biologics, adequate samples for the examination of any product or ingredient used in its manufacture.

(f) Bring to the attention of the manufacturer any fault observed in the course of inspection in location, construction, manufacturing methods, or administration of a licensed establishment which might lead to impairment of a product.

(g) Inspect and copy, as circumstances may require, any records required to be kept pursuant to §600.12.

(h) Certify as to the condition of the establishment and of the manufacturing methods followed and make recommendations as to action deemed appropriate with respect to any application for license or any license previously issued.

PART 601—LICENSING

Subpart A—General Provisions

Sec.

601.1 Two forms of licenses.
601.2 Application for establishment and product licenses; procedure for filing.

enclosures, and containers proposed to be used for the product. An application for license shall not be considered as filed until all pertinent information and data shall have been received from the manufacturer by the Bureau of Biologics. The applicant shall also include an environmental impact analysis report analyzing the environmental impact of the manufacturing process and the ultimate use or consumption of the biological product pursuant to §25.1 of this chapter. In lieu of the procedures described in this paragraph, applications for radioactive biological products shall be handled as set forth in paragraph (b) of this section.

* * * * *

§601.3 License forms.

(a) *Establishment license.* The establishment license form shall be prescribed by the Commissioner of Food and Drugs and shall include:

(1) The name and address of the manufacturer.

(2) The name and address of the establishment.

(3) The names and addresses of all locations of the establishment.

(4) The license number.

(5) The date of issuance.

(b) *Product license.* The product license form shall be prescribed by the Commissioner of Food and Drugs and shall include:

(1) The name and address of the manufacturer.

(2) The name and address of the establishment.

(3) The name and address of each location at which the product is manufactured.

(4) The license number of the establishment.

(5) The proper name of the product, with additional specifications, if any, which may be approved or required for additional labeling purposes.

§601.4 Issuance and denial of license.

(a) An establishment or product license shall be issued upon a determination by the Commissioner that the establishment or the product, as the case may be, meets the applicable standards established in this chapter. Licenses shall be valid until suspended or revoked.

(b) If the Commissioner determines that the establishment or product does not meet the standards established in this chapter, he shall deny the application and inform the applicant of the grounds for, and of an opportunity for a hearing on, his decision. If the applicant so requests, the Commissioner shall issue a notice of opportunity for hearing on the matter pursuant to §12.21(b) of this chapter.

[42 FR 4718, Jan. 25, 1977, as amended at 42 FR 15676, Mar. 22, 1977; 42 FR 19142, Apr. 12, 1977]

§601.5 Revocation of license.

(a) An establishment or product license shall be revoked upon application of the manufacturer giving notice of intention to discontinue the manufacture of all products or to discontinue the manufacture of a particular product for which a license is held, and waiving an opportunity for a hearing on the matter.

(b) If the Commissioner finds that (1) authorized Food and Drug Administration employees after reasonable efforts have been unable to gain access to an establishment or a location for the purpose of carrying out the inspection required under §600.21 of this chapter. (2) manufacturing of products or of a product has been discontinued to an extent that a meaningful inspection or evaluation cannot be made, (3) the manufacturer has failed to report a change as required by §601.12, (4) the establishment or any location thereof, or the product for which the license has been issued, fails to conform to the applicable standards established in the license and in this chapter designed to ensure the

continued safety, purity, and potency of the manufactured product, (5) the establishment or the manufacturing methods have been so changed as to require a new showing that the establishment or product meets the standards established in this chapter in order to protect the public health, or (6) the licensed product is not safe and effective for all of its intended uses or is misbranded with respect to any such use, he shall notify the licensee of his intention to revoke the license, setting forth the grounds for, and offering an opportunity for a hearing on, the proposed revocation. Except as provided in §601.6 and in cases involving willfulness, the notification required in this paragraph shall provide a reasonable period for the licensee to demonstrate or achieve compliance with the requirements of this chapter, before proceedings will be instituted for the revocation of the license. If compliance is not demonstrated or achieved and the licensee does not waive the opportunity for a hearing, the Commissioner shall issue a notice of opportunity for hearing on the matter pursuant to §12.21(b) of this chapter.

[42 FR 4718, Jan. 25, 1977, as amended at 42 FR 15676, Mar. 22, 1977; 42 FR 19143, Apr. 12, 1977]

§601.6 Suspension of license.

(a) Whenever the Commissioner has reasonable grounds to believe that any of the grounds for revocation of a license exist and that by reason thereof there is a danger to health, he may notify the licensee that his license for the establishment or the product is suspended and require that the licensee (1) notify the selling agents and distributors to whom such product or products have been delivered of such suspension, and (2) furnish to the Director, Bureau of Biologics, complete records of such deliveries and notice of suspension.

(b) Upon suspension of a license, the Commissioner shall either (1) proceed pursuant to the provisions

of §601.5(b) to revoke the license, or (2) if the licensee agrees, hold revocation in abeyance pending resolution of the matters involved.

[42 FR 4718, Jan. 25, 1977]

§601.7 Procedure for hearings.

(a) A notice of opportunity for hearing, notice of appearance and request for hearing, and grant or denial of hearing for a biological drug pursuant to this Part, for which the exemption from the Federal Food, Drug, and Cosmetic Act in §310.4 of this chapter has been revoked, shall be subject to the provisions of §314.200 of this chapter except to the extent that the notice of opportunity for hearing on the matter issued pursuant to §12.21(b) of this chapter specifically provides otherwise.

(b) Hearings pursuant to §§601.4 through 601.6 shall be governed by Part 12 of this chapter.

(c) When a license has been suspended pursuant to §601.6 and a hearing request has been granted, the hearing shall proceed on an expedited basis.

[42 FR 4718, Jan. 25, 1977, as amended at 42 FR 15676, Mar. 22, 1977; 42 FR 19143, Apr. 12, 1977]

§601.8 Publication of revocation.

Notice of revocation of a license, with statement of the cause therefor, shall be issued by the Commissioner and published in the FEDERAL REGISTER.

[42 FR 4718, Jan. 25, 1977]

§601.9 Licenses; reissuance.

(a) *Compliance with standards.* An establishment or product license, previously suspended or revoked,

may be reissued or reinstated upon a showing of compliance with required standards and upon such inspection and examination as may be considered necessary by the Commissioner.

(b) *Exclusion of noncomplying location.* An establishment or product license, excluding a location or locations that fail to comply with required standards, may be issued without further application and concurrently with the suspension or revocation of the license for noncompliance at the excluded location or locations.

[42 FR 4716, Jan. 25, 1977]

Subpart B—Establishment Licensing

§601.10 Establishment licenses; issuance and conditions.

(a) *Inspection—compliance with standards.* An establishment license shall be issued only after inspection of the establishment and upon a determination that the establishment complies with the applicable standards prescribed in the regulations in this subchapter.

(b) *Availability of product; simultaneous request for and issuance of product license.* No establishment license shall be issued unless (1) a product intended for sale, barter or exchange or intended to be offered, sent, carried or brought for sale, barter or exchange is available for examination, (2) such product is available for inspection during all phases of manufacture and (3) a product license is requested and issued simultaneously with the establishment license.

(c) *One establishment license to cover all locations.* One establishment license shall be issued to cover all locations meeting the establishment standards.

§601.12 Changes to be reported.

(a) *General.* Important proposed changes in location, equipment, management and responsible personnel, or in manufacturing methods and labeling, of any

product for which a license is in effect or for which an application for license is pending, shall be reported to the Director, Bureau of Biologics, by the manufacturer, and unless in case of emergency, not less than 30 days in advance of the time such changes are intended to be made.

(b) *Manufacturing methods and labeling.* Proposed changes in manufacturing methods and labeling may not become effective until notification of acceptance is received from the Director, Bureau of Biologics.

[38 FR 32052, Nov. 20, 1973. Redesignated and amended at 42 FR 4718, Jan. 26, 1977]

Subpart C—Product Licensing

§601.20 Product licenses; issuance and conditions.

(a) *Examination—compliance with standards.* A product license shall be issued only upon examination of the product and upon a determination that the product complies with the standards prescribed in the regulations in this subchapter: *Provided,* That no product license shall be issued upon a determination that the establishment complies with the establishment standards prescribed in the regulations contained in this subchapter, applicable to the manufacture of such product.

(b) *Manufacturing process—impairment of assurances.* No product shall be licensed if any part of the process of or relating to the manufacture of such product, in the judgment of the Commissioner of Food and Drugs, would impair the assurances of continued safety, purity and potency as provided by the regulations contained in this subchapter.

§601.21 Products under development.

A biological product or trivalent organic arsenical undergoing development, but not yet ready for a product

license, may be shipped or otherwise delivered from one State or possession into another State or possession provided such shipment or delivery is not for sale, barter or exchange and is in accordance with section 505 of the Federal Food, Drug, and Cosmetic Act, as amended, and the regulations thereunder.

§601.22 Products in short supply; initial manufacturing at other than licensed establishment.

Licenses issued to a manufacture for an establishment shall authorize persons other than such manufacturer to conduct at places other than such establishment the initial, and partial manufacturing of a product for shipment solely to such manufacturer only to the extent that the names of such persons and places are registered with the Commissioner of Food and Drugs and he finds upon application of such manufacturer, that (a) the product is in short supply due either to the peculiar requirements of the organism involved or to the scarcity of the animal required for manufacturing purposes, and (b) such manufacturer has established with respect to such persons and places such procedures, inspections, tests or other arrangements as will assure full compliance with the applicable regulations of this subchapter related to continued safety, purity, and potency. Such persons and places shall be subject to all regulations of this subchapter except §§601.1 to 601.6, 601.9, 601.10, 601.20, 6091.21, 601.30 to 601.33 and 610.60 to 610.65 of this chapter. Failure of such manufacturer to maintain such procedures, inspections, tests, or other arrangements, or failure of any person conducting such partial manufacturing to comply with applicable regulations shall constitute a ground for suspension or revocation of the authority conferred pursuant to this section on the same basis as provided in §§601.6 to 601.8 with respect to the suspension and the revocation of licenses.

[42 FR 4718, Jan. 25, 1977]

§601.25 Review procedures to determine that licensed biological products are safe, effective, and not misbranded under prescribed, recommended, or suggested conditions of use.

For purposes of reviewing biological products that have been licensed prior to July 1, 1972, to determine that they are safe and effective and not misbranded, the following regulations shall apply. Prior administrative action exempting biological products from the provisions of the Federal Food, Drug, and Cosmetic Act is superseded to the extent that these regulations result in imposing requirements pursuant to provisions therein for a designated biological product or category of products.

(a) *Advisory review panels.* The Commissioner of Food and Drugs shall appoint advisory review panels (1) to evaluate the safety and effectiveness of biological products for which a license has been issued pursuant to section 351 of the Public Health Service Act, (2) to review the labeling of such biological products, and (3) to advise him on which of the biological products under review are safe, effective, and not misbranded. An advisory review panel shall be established for each designated category of biological product. The members of a panel shall be qualified experts, appointed by the Commissioner, and shall include persons from lists submitted by organizations representing professional, consumer, and industry interests. Such persons shall represent a wide divergence of responsible medical and scientific opinion. The Commissioner shall designate the chairman of each panel, and summary minutes of all meetings shall be made.

(b) *Request for data and views.* (1) The Commissioner of Food and Drugs will publish a notice in the FEDERAL REGISTER requesting interested persons to submit, for review and evaluation by an advisory review

or other conditions necessary or appropriate for their safety and effectiveness.

(2) A statement which designates those biological products determined by the panel to be unsafe or ineffective, or to be misbranded. The statement shall include the panel's reasons for each such determination.

(3) A statement which designates those biological products determined by the panel not to fall within either paragraphs (e)(1) or (2) of this section on the basis of the panel's conclusion that the available data are insufficient to classify such biological products, and for which further testing is therefore required. The report shall recommend with as must specificity as possible the type of further testing required and the time period within which it might reasonably be concluded. The report shall also recommend whether the product license should or should not be revoked, thus permitting or denying continued manufacturing and marketing of the biological product pending completion of the testing. This recommendation will be based on an assessment of the present evidence of the safety and effectiveness of the product and the potential benefits and risks likely to result from the continued use of the product for a limited period of time while the questions raised concerning the product are being resolved by further study.

(f) *Proposed order.* After reviewing the conclusions and recommendations of the advisory review panel, the Commissioner of Food and Drugs shall publish in the FEDERAL REGISTER a proposed order containing:

(1) A statement designating the biological products in the category under review that are determined by the Commissioner of Food and Drugs to be safe and effective and not misbranded. This statement may include any condition relating to active components, labeling, tests required prior to release of lots, product standards, or other conditions necessary or appropriate for their

safety and effectiveness, and may propose corresponding amendments in other regulations under this Subchapter F.

(2) A statement designating the biological products in the category under review that are determined by the Commissioner of Food and Drugs to be unsafe or ineffective, or to be misbranded, together with the reasons therefor. All licenses for such products shall be proposed to be revoked.

(3) A statement designating the biological products not included in either of the above two statements on the basis of the Commissioner of Food and Drugs determination that the available data are insufficient to classify such biological products under either paragraphs (f) (1) or (2) of this section. Licenses for such products may be proposed to be revoked or to remain in effect on an interim basis. Where the Commissioner determines that the potential benefits outweigh the potential risks, the proposed order shall provide that the product license for any biological product, falling within this paragraph will not be revoked but will remain in effect on an interim basis while the data necessary to support its continued marketing are being obtained for evaluation by the Food and Drug Administration. The tests necessary to resolve whatever safety or effectiveness questions exist shall be described.

(4) The full report or reports of the panel to the Commissioner of Food and Drugs.

The summary minutes of the panel meeting or meetings shall be made available to interested persons upon request. Any interested person may within 90 days after publication of the proposed order in the FEDERAL REGISTER, file with the Hearing Clerk of the Food and Drug Administration written comments in quintuplicate. Comments may be accompanied by a memorandum or brief in support thereof. All comments may be reviewed at the office of the Hearing Clerk during regular working hours, Monday through Friday.

VI. Efficacy data.

A. Individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination on the efficacy of each individual active component.

5. Pertinent medical and scientific literature.

B. Combinations of the individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination as to the effectiveness of combinations of the individual active components.

5. Pertinent medical and scientific literature.

C. Finished biological product.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination as to the effectiveness of the finished biological product.

5. Pertinent medical and scientific literature.

VII. A summary of the data and views setting forth the medical rational and purpose (or lack thereof) for the biological product and its components and the scientific basis (or lack thereof) for the conclusion that the biological product, including its components, has been proven safe and effective and is properly labeled for the intended use or uses. If there is an absence of controlled studies in the materials submitted, an explanation as to why such studies are not considered necessary or feasible shall be included.

VIII. If the submission is by a licensee, a statement signed by the responsible head (as defined in §600.10 of

this chapter) of the licensee shall be included, stating that to the best of his knowledge and belief, it includes all information, favorable and unfavorable, pertinent to an evaluation of the safety, effectiveness, and labeling of the product, including information derived from investigation, commercial marketing, or published literature. If the submission is by an interested person other than a licensee, a statement signed by the person responsible for such submission shall be included, stating that to the best of his knowledge and belief, it fairly reflects a balance of all the information, favorable and unfavorable, available to him pertinent to an evaluation of the safety, effectiveness, and labeling of the product.

(c) *Deliberations of an advisory review panel.* An advisory review panel will meet as often and for as long as is appropriate to review the data submitted to it and to prepare a report containing its conclusions and recommendations to the Commissioner of the Food and Drugs with respect to the safety, effectiveness, and labeling of the biological products in the designated category under review.

(1) A panel may also consult any individual or group.

(2) Any interested person may request in writing an opportunity to present oral views to the panel. Such written requests for oral presentations should include a summarization of the data to be presented to the panel. Such requests may be granted or denied by the panel.

(3) Any interested person may present written data and views which shall be considered by the panel. This information shall be presented to the panel in the format set forth in paragraph (b)(3) of this section and within the time period established for the biological product category in the notice for review by a panel.

(d) *Standards for safety, effectiveness, and labeling.* The advisory review panel, in reviewing the submitted data and preparing the panel's conclusions and recommendations, and the Commissioner of Food and

(g) *Final order.* After reviewing the comments, the Commissioner of Food and Drugs shall publish in the FEDERAL REGISTER a final order on the matters covered in the proposed order. The final order shall become effective as specified in the order.

(h) *Additional studies and labeling.* (1) Within 30 days following publication of the final order, each licensee for a biological product designated as requiring further study to justify continued marketing on an interim basis, pursuant to paragraph (f)(3) of this section, shall satisfy the Commissioner of Food and Drugs in writing that studies adequate and appropriate to resolve the questions raised about the product have been undertaken, or the Federal Government may undertake the studies. The Commissioner may extend this 30-day period if necessary, either to review and act on proposed protocols or upon indication from the licensee that the studies will commence at a specified reasonable time. If no such commitment is made, or adequate and appropriate studies are not undertaken, the product license or licenses shall be revoked.

(2) A progress report shall be filed on the studies every January 1 and July 1 until completion. If the progress report is inadequate or if the Commissioner of Food and Drugs concludes that the studies are not being pursued promptly and diligently, or if interim results indicate the potential benefits do not outweigh the potential risks, the product license or licenses shall be revoked.

(3) Promptly upon completion of the studies undertaken on the product, the Commissioner of Food and Drugs will review all available data and will either retain or revoke the product license or licenses involved. In making this review and evaluation the Commissioner may again consult the advisory review panel which prepared the report on the product, or other advisory committees, professional organizations, or experts. The

Commissioner shall take such action by notice published in the FEDERAL REGISTER.

(4) Labeling and promotional material for Bacterial Vaccines and Bacterial Antigens with "No U.S. Standard of Potency" requiring additional studies shall bear a box statement in the following format:

> Based on a review by the Panel on Review of *(insert name of appropriate panel)* and other information, the Food and Drug Administration has directed that further investigation be conducted before this product is determined to be fully effective for labeled indication(s).

(5) A written informed consent shall be obtained from participants in the requisite additional studies for Bacterial Vaccines and Bacterial Antigens with "No U.S. Standard of Potency" explaining the nature of the product and the investigation. The explanation shall consist of such disclosure and be so made that intelligent and informed consent be given, and that a clear opportunity to refuse is presented.

(i) *Court Appeal.* The final order(s) published pursuant to paragraph (g) of this section, and any notice published pursuant to paragraph (h) of this section, constitute final agency action from which appeal lies to the courts. The Food and Drug Administration will request consolidation of all appeals in a single court. Upon court appeal, the Commissioner of Food and Drugs may, at his discretion, stay the effective date for part or all of the final order or notice, pending appeal and final court adjudication.

(Secs. 201, 502, 505, 701, 52 Stat. 1040-1042 as amended. 1050-1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371); sec. 351, 58 Stat. 702 as amended

panel, published and unpublished data and information pertinent to a designated category of biological products.

(2) Data and information submitted pursuant to a published notice, and falling within the confidentiality provisions of 18 U.S.C. 1905, 5 U.S.C. 552(b), or 21 U.S.C. 331(j), shall be handled by the advisory review panel and the Food and Drug Administration as confidential until publication of a proposed evaluation of the biologics under review and the full report or reports of the panel. Thirty days thereafter such data and information shall be made available and may be viewed at the office of the Hearing Clerk of the Food and Drug Administration, except to the extent that the person submitting it demonstrates that it still falls within the confidentiality provisions of one or more of those statutes.

(3) To be considered, 12 copies of the submission on any marketed biological product within the class shall be submitted, preferably bound, indexed, and on standard sized paper, approximately 8½ x 11 inches. The time alloted for submissions will be 60 days, unless otherwise indicated in the specific notice requesting data and views for a particular category of biological products. When requested, abbreviated submissions should be sent. All submissions shall be in the following format, indicating "none" or "not applicable" where appropriate, unless changed in the FEDERAL REGISTER notice:

BIOLOGICAL PRODUCTS REVIEW INFORMATION

I. Label or labels and all other labeling (preferably mounted. Facsimile labeling is acceptable in lieu of actual container labeling), including labeling for export.

II. Representative advertising used during the past 5 years.

III. The complete quantitative composition of the biological product.

IV. Animal safety data.

A. Individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

B. Combinations of the individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

C. Finished biological product.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

V. Human safety data.

A. Individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination as to the safety of each individual active component.

5. Pertinent medical and scientific literature.

B. Combinations of the individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination as to the safety of combinations of the individual active components.

5. Pertinent medical and scientific literature.

C. Finished biological product.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination as to the safety of the finished biological product.

5. Pertinent medical and scientific literature.

Drugs, in reviewing and implementing the conclusions and recommendations of the panel, shall apply the following standards to determine that a biological product is safe and effective and not misbranded.

(1) Safety means the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time. Proof of safety shall consist of adequate test by methods reasonably applicable to show the biological product is safe under the prescribed conditions of use, including results of significant human experience during use.

(2) Effectiveness means a reasonable expectation that, in a significant proportion of the target population, the pharmacological or other effect of the biological product, when used under adequate directions, for use and warnings against unsafe use, will serve a clinically significant function in the diagnosis, cure, mitigation, treatment, or prevention of disease in man. Proof of effectiveness shall consist of controlled clinical investigations as defined in §314.111(a)(5)(ii) of this chapter, unless this requirement is waived on the basis of a showing that it is not reasonably applicable to the biological product or essential to the validity of the investigation, and that an alternative method of investigation is adequate to substantiate effectiveness. Alternate methods, such as serological response evaluation in clinical studies and appropriate animal and other laboratory assay evaluations may be adequate to substantiate effectiveness where a previously accepted correlation between data generated in this way and clinical effectiveness already exists. Investigations may be corroborated by partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and

reports of significant human experience during marketing. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered.

(3) The benefit-to-risk ratio of a biological product shall be considered in determining safety and effectiveness.

(4) A biological product may combine two or more safe and effective active components: (i) When each active component makes a contribution to the claimed effect or effects; (ii) when combining of the active ingredients does not decrease the purity, potency, safety, or effectiveness of any of the individual active components; and (iii) if the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent preventive therapy or treatment for a significant proportion of the target population.

(5) Labeling shall be clear and truthful in all respects and may not be false or misleading in any particular. It shall comply with section 351 of the Public Health Service Act and sections 502 and 503 of the Federal Food, Drug, and Cosmetic Act, and in particular with the applicability requirements of §§610.60 through 610.65 and Subpart D of Part 201 of this chapter.

(e) *Advisory review panel report to the Commissioner.* An advisory review panel shall submit to the Commissioner of Food and Drugs a report containing the panel's conclusions and recommendations with respect to the biological products falling within the category covered by the panel. Included within this report shall be:

(1) A statement which designates those biological products determined by the panel to be safe and effective and not misbranded. This statement may include any condition relating to active components, labeling, tests required prior to release of lots, product standards,

(42 U.S.C. 262); secs. 4, 10, 60 Stat. 238 and 242 as amended (5 U.S.C. 553, 702, 703, 704))
[38 FR 32052, Nov. 20, 1973, as amended at 39 FR 11535, Mar. 29, 1974; 40 FR 13496, Mar. 27, 1975; 43 FR 44838, Sept. 29, 1978; 44 FR 1549, Jan. 5, 1979]

EFFECTIVE DATE NOTE: The labeling requirements in §601.25(h)(4) and (5) become effective July 5, 1979. See 44 FR 1549, Jan. 5, 1979.

Subpart E—[Reserved]

Part 610—GENERAL BIOLOGICAL PRODUCTS STANDARDS

Subpart A—Release Requirements

Sec.
610.1 Tests prior to release required for each lot.
610.2 Requests for samples and protocols; official release.

Subpart B—General Provisions

610.10 Potency.
610.11 General safety.
610.11a Inactivated influenza vaccine, general safety test.
610.12 Sterility.
610.13 Purity.
610.14 Identity.
610.15 Constituent materials.
610.16 Total solids in serums.
610.17 Permissible combinations.
610.18 Cultures.
610.19 Status of specific products; Group A streptococcus.

Subpart C—Standard Preparations and Limits of Potency

610.20 Standard preparations.
610.21 Limits of potency.

Subpart D—Mycoplasma

610.30 Test for Mycoplasma.

Subpart E—Hepatitis Requirements

610.40 Test for hepatitis B surface antigen.
610.41 History of hepatitis B surface antigen.

Subpart F—Dating Period Limitations

610.50 Date of manufacture.
610.51 Periods of cold storage.
610.52 Dating period.
610.53 Dating periods for specific products.

Subpart G—Labelling Standards

610.60 Container label.
610.61 Package label.
610.62 Proper name; package label; legible type.
610.63 Divided manufacturing responsibility to be shown.
610.64 Name of selling agent or distributor.
610.65 Products for export.

AUTHORITY: Sec. 215, 58 Stat. 690, as amended: 42 U.S.C. 216, Sec. 351, 58 Stat. 702, as amended; 42 U.S.C. 262, unless otherwise noted.

SOURCE: 38 FR 32056, Nov. 20, 1973, unless otherwise noted.

CROSS REFERENCES: For U.S. Customs Service regulations relating to viruses, serums, and toxins, see 19 CFR 12.21-12.23. For U.S. Postal Service regulations relating to the admissibility to the United States mails see Parts 124 and 125 of the Postal Service Manual, this is incorporated by reference in 39 CFR Part 111.

Subpart A—Release Requirements

§610.1 Tests prior to release required for each lot.

No lot of any licensed product shall be released by the manufacturer prior to the completion of tests for conformity with standards applicable to such product. Each applicable test shall be made on each lot after completion of all processes of manufacture which may affect compliance with the standard to which the test applies. The results of all tests performed shall be considered in determinating whether or not the test results meet the test objective, except that a test result may be disregarded when it is established that the test is invalid due to causes unrelated to the product.

§610.2 Requests for samples and protocols; official release.

(a) *General.* Samples of any lot of any licensed product, except for radioactive biological products, together with the protocols showing results of applicable tests, may at any time be required to be sent to the Director, Bureau of Biologics. Upon notification by the Director, Bureau of Biologics, a manufacturer shall not distribute a lot of a product until the lot is released by the Director, Bureau of Biologics: *Provided,* That the Director, Bureau of Biologics, shall not issue such notification except when deemed necessary for the safety, purity, or potency of the product.

Subpart B—General Provisions

§610.10 Potency.

Tests for potency shall consist of either in vitro or in vivo tests, or both, which have been specifically designed for each product so as to indicate its potency in a manner adequate to satisfy the interpretation of potency given by the definition in §600.3(s) of this chapter.

§610.11 General safety.

A general safety test for the detection of extraneous toxic contaminants shall be performed on biological products intended for administration to humans. The general safety test is required in addition to other specific tests prescribed in the additional standards for individual products in this subchapter, except that, the test need not be performed on those products listed in paragraph (g) of this section. The general safety test shall be performed as specified in this section, unless: Modification is prescribed in the additional standards for specific products, or variation is approved as an amendment to the product license under paragraph (f) of this section.

(a) *Product to be tested.* The general safety test shall be conducted upon a representative sample of the product in the final container from every final filling of each lot of the product. If any product is processed further after filling, such as by freeze-drying, sterilization, or heat treatment, the test shall be conducted upon a sample from each filling of each drying chamber run, sterilization chamber, or heat treatment bath.

(b) *Test animals.* Only overtly healthy guinea pigs weighting less than 400 grams each and mice weighting less than 22 grams each shall be used. The animals shall not have been used previously for any test purpose.

(c) *Procedure.* The duration of the general safety test shall be 7 days for both species, except that a longer period may be established for specific products in accordance with paragraph (f) of this section. Once the manufacturer has established a specific duration of the test period for a specific product, it cannot be varied subsequently, except, in accordance with paragraph (f) of this section. Each test animal shall be weighed and the individual weights recorded immediately prior to injection and on the last day of the test. Each animal

shall be observed every working day. Any animal response including any which is not specific for or expected from the product and which may indicate a difference in its quality shall be recorded on the day such response is observed. The test product shall be administered as follows:

(1) *Liquid product or freeze-dried product which has been reconstituted as directed on the label.* Inject intraperitoneally 0.5 milliliter of the liquid product or the reconstituted product into each of at least two mice, and 5.0 milliliters of the liquid product or the reconstituted product into each of at least two guinea pigs.

(d) *Test requirements.* A safety test is satisfactory if all animals meet all of the following requirements:

(1) They survive the test period.

(2) They do not exhibit any response which is not specific for or expected from the product and which may indicate a difference in its quality.

(3) They weigh no less at the end of the test period than at the time of injection.

(e) *Repeat tests*—(1) *First repeat test.* If a filling fails to meet the requirements of paragraph (d) of this section in the initial test, a repeat test may be conducted on the species which failed the initial test, as prescribed in paragraph (c) of this section. The filling is satisfactory only if each retest animal meets the requirements prescribed in paragraph (d) of this section.

(2) *Second repeat test.* If a filling fails to meet the requirements of the first repeat test, a second repeat test may be conducted on the species which failed the test: *Provided,* That 50 percent of the total number of animals in that species has survived the initial and first repeat tests. The second repeat test shall be conducted as prescribed in paragraph (c) of this section, except that the number of animals shall be twice that used in the first repeat test. The filling is satisfactory only if each

second repeat test animal meets the requirements prescribed in paragraph (d) of this section.

(f) *Test variations.* Variations in the general safety test, such as test dose, route of administration, or duration of the test period may be offered as an amendment to the product license and must receive written approval by the Director, Bureau of Biologics, Food and Drug Administration. Approval will be given only if the license amendment provides substantial evidence demonstrating that the proposed test variation will assure sensitivity equal to or greater than the test prescribed in this section.

(g) *Exceptions.* The test prescribed in this section need not be performed for Whole Blood (Human), Red Blood Cells (Human), Cryoprecipitated Antihemophilic Factor (Human), Platelet Concentrate (Human), or Single Donor Plasma (Human).

[41 FP 10691, Mar. 15, 1976]

§610.11a Inactivated Influenza vaccine, general safety test.

For inactivated influenza vaccine, the general safety test shall be conducted in the manner indicated in §610.11 of this chapter except that, with reference to guinea pigs, the test shall be satisfied if the product provides satisfactory results using either the subcutaneous or intraperitoneal injection of 5.0 milliliters of inactivated influenza vaccine into each guinea pig. The requirements for general safety for inactivated influenza vaccine shall not be considered to be satisfied unless each lot of influenza vaccine is assayed for endotoxin in comparison to a reference preparation provided by the Food and Drug Administration, and such lot is found to contain no more endotoxin than the reference preparation.

[39 FR 40016, Nov. 13, 1974]

§610.12 Sterility.

Except as provided in paragraphs (f) and (g) of this section, the sterility of each lot of each product shall be demonstrated by the performance of the tests prescribed in paragraphs (a) and (b) of this section for both bulk and final container material.

(a) *The test.* Bulk material shall be tested separately from final container material and material from each final container shall be tested in individual test vessels as follows:

(1) *Using Fluid Thioglycollate Medium*—(1) *Bulk and final container material.* The volume of product, as required by paragraph (d) of this section (hereinafter referred to also as the "inoculum"), from samples of both bulk and final container material, shall be inoculated into test vessels of Fluid Thioglycollate Medium. The inoculum and medium shall be mixed thoroughly and incubated at a temperature of 30° to 32° C. for a test period of no less than 14 days and examined visually for evidence of growth on the third, fourth or fifth day and on the seventh or eighth day and on the last day of the test period. Results of each examination shall be recorded. If the inoculum renders the medium turbid so that the absence of growth cannot be determined reliably by visual examination, portions of this turbid medium in amounts of no less than 1.0 ml. shall be transferred on the third, fourth, or fifth day of incubation, from each of the test vessels and inoculated into additional vessels of medium. The material in the additional vessels shall be incubated at a temperature of 30° to 32° C. for no less than 14 days. Notwithstanding such transfer of material, examination of the original vessels shall be continued as prescribed above. The additional test vessels shall be examined visually for evidence of growth on the third, fourth, or fifth day of incubation and on the seventh or eighth day and on the last day of the incubation period. If growth appears, repeat tests

may be performed as prescribed in paragraph (b) of this section and interpreted as specified in paragraph (c) of this section.

(ii) *Final container material containing a mercurial preservative.* In addition to the test prescribed in paragraph (a)(1)(i) of this section, final container material containing a mercurial preservative shall be tested using Fluid Thioglycollate Medium following the procedures prescribed in such subparagraph, except that the incubation shall be at a temperature of 20° to 25° C.

(2) *Using Soybean-Casein Digest Medium.* Except for products containing a mercurial preservative, a test shall be made on final container material, following the procedures prescribed in paragraph (a)(1)(i) of this section, except that the medium shall be Soybean-Casein Digest Medium and the incubation shall be at a temperature of 20° to 25° C.

(b) *Repeat tests.* If growth appears in any of the test media during testing of either bulk or final container material, the test may be repeated to rule out faulty test procedures as follows:

(1) *Repeat bulk test.* Only one repeat bulk test may be conducted. The volume of inoculum to be used for the repeat bulk test shall be as prescribed in paragraph (d)(1) of this section. The repeat test shall be performed using the procedure prescribed in paragraph (a)(1)(i) of this section.

(2) *First repeat final container test.* The number of test samples and the volumes of product used for the first repeat test shall be as prescribed in paragraph (d)(2) of this section. For products that do not contain a mercurial preservative, the repeat test shall be performed, using both Fluid Thioglycollate Medium and Soybean-Casein Digest Medium, following the procedures prescribed in paragraphs (a)(1)(i) and (a)(2), respectively, of this section. If the product contains a

mercurial preservative, the repeat test shall be performed using Fluid Thioglycollate Medium and the procedures prescribed in paragraph (a)(1)(i) and (ii) of this section.

(3) *Second repeat final container test.* If growth appears in any of the first repeat final container tests, all tests of the first repeat final container test shall be repeated, provided there was no evidence of growth in any test of the bulk material. The test samples used for the second repeat final container test shall be twice the number used for the first repeat final container test.

(c) *Interpretation of test results.* The results of all tests performed on a lot shall be considered in determining whether or not the lot meets the requirements for sterility, except that tests may be excluded when demonstrated by adequate controls to be invalid. The lot meets the test requirements if no growth appears in the tests prescribed in paragraph (a) of this section. If repeat tests are performed, the lot meets the test requirements if no growth appears in the tests prescribed in paragraph (b)(2) or (3) of this section, whichever is applicable.

(d) *Test samples and volumes*—(1) *Bulk.* Each sample for the bulk sterility test shall be representative of the bulk material and the volume tested shall be no less than 10 ml. (Note exceptions in paragraph (g) of this section.)

(2) *Final containers.* The sample used for each test medium or each incubation temperature of a test medium for the final container and first repeat final container test shall be no less than 20 final containers from each filling of each lot, selected to represent all stages of filling from the bulk vessel. If the amount of material in the final container is 1.0 milliliter or less, the entire contents shall be tested. If the amount of material in the final container is more than 1.0 milliliter, the

volume tested shall be the largest single dose recommended by the manufacturer or 1.0 milliliter, whichever is larger, but no more than 10 milliliters of material or the entire contents from a single final container need be tested. If more than 2 filling machines, each with either single or multiple filling stations, are used for filling one lot, no less than 10 filled containers shall be tested from each filling machine for each test medium or each incubation temperature condition, but no more than 100 containers of each lot need be tested. The items tested shall be representative of each filling assembly and shall be selected to represent all stages of the filling operation. (Note exceptions in paragraph (g) of this section.)

(e) *Culture medium*—(1) *Formulae.* (i) The formula for Fluid Thioglycollate Medium is as follows:

[Table Omitted]

(2) *Culture media requirements*—(i) *Growth prompting qualities.* Each lot of dehydrated medium bearing the manufacturer's identifying number, or each lot of medium prepared from basic ingredients, shall be tested for its growth-promoting qualities using not more than 100 organisms of two or more strains of microorganisms that are exacting in their nutritive and aerobic-anaerobic requirements.

(ii) *Conditions of medium and design of test vessels.* A medium shall not be used if the extent of evaporation affects its fluidity, nor shall it be reused in a sterility test. Fluid Thioglycollate Medium shall not be used if more than the upper one-third has acquired a pink color. The medium may be restored once by heating on a steam bath or in free-flowing steam until the pink color disappears. The design of the test vessel for Fluid Thioglycollate Medium shall be such as is shown to provide favorable aerobic and anaerobic growth of microorganisms throughout the test period.

(iii) *Ratio of the inoculum to culture medium.* The ratio of the inoculum to the volume of the culture

medium resulting in a dilution of the product that is not bacteriostatic or fungistatic shall be determined for each product, except for those tested by membrane filtration. Vessels of the product-medium mixture(s) and control vessels of the medium shall be inoculated with dilutions of cultures of bacteria or fungi which are sensitive to the product being tested, and incubated at the appropriate temperature for no less than 7 days. Inhibitors or neutralizers of preservatives may be considered in determining the proper ratio.

(f) *Membrane filtration.* Bulk and final container material or products containing oil or products in water insoluble ointments shall be tested for sterility using the membrane filtration procedure set forth in the United States Pharmacopeia[1] (19th Revision, 1975), section entitled "Membrane Filtration," pages 594-595, except that (1) the test samples shall conform with paragraph (d) of this section; (2) the temperature of incubation for the test using Fluid Thioglycollate Medium shall be 30° to 32° C; and (3) in addition, for products containing a mercurial preservative, the product shall be tested in a second test using Fluid Thioglycollate Medium incubated at 20° to 25° C in lieu of the test in Soybean-Casein digest Medium. Such Membrane Filtration section is hereby incorporated by reference and deemed published herein. The United States Pharmacopeia is available at most medical and public libraries and copies of the pertinent section will be provided to any manufacturer affected by the provisions of this subchapter upon request to the Director, Bureau of Biologics or the appropriate Information Center Offices listed in 45 CFR Part 5. In addition, an official historic file of the material incorporated by reference is maintained in the office of the Director, Bureau of Biologics.

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1. Copies may be obtained from: United States Pharmacopeial Convention, Inc. 12601 Twinbrook Parkway, Rockville, Md. 20852

(g) *Exceptions.* Bulk and final container material shall be tested for sterility as described above in this section, except as follows:

(1) *Different sterility tests prescribed.* When different sterility tests are prescribed for a product in this subchapter.

(2) *Alternate incubation temperatures.* Two tests may be performed, in all respects as prescribed in paragraph (a)(1)(i) of this section, one test using an incubation temperature of 18° to 22° C., the other test using an incubation temperature of 35° to 37° C., in lieu of performing one test using an incubation temperature of 30° to 32° C.

(3) *Different tests equal or superior.* A different test (such as membrane filtration as set forth in paragraph (f) of this section) may be performed provided that prior to the performance of such test a manufacturer submits data which the Commissioner of Food and Drugs finds adequate to establish that the different test is equal or superior to the tests described in paragraphs (a) and (b) of this section in detecting contamination and makes the finding a matter of official record.

(4) *Test precluded or not required.* The tests prescribed in this section need not be performed for Whole Blood (Human), Cryoprecipitated Antihemophilic Factor (Human), Platelet Concentrate (Human), Leukocyte Typing Serum, Red Blood Cells (Human), Single Donor Plasma (Human), Source Plasma (Human), Smallpox Vaccine, Reagent Red Blood Cells, and other similar products concerning which the Commissioner of Food and Drugs finds that the mode of administration, the method of preparation, or the special nature of the product precludes or does not require a sterility test.

(5) *Number of final containers more than 20, less than 200.* If the number of final containers in the filling is more than 20 or less than 200, the sample shall be no less than 10 percent of the containers.

(6) *Number of final containers—20 or less.* If the number of the final containers in a filling is 20 or less, the sample shall be two final containers, or the sample need be no more than one final container, provided (i) the bulk material met the sterility test requirements and (ii) after filling, it is demonstrated by testing a simulated sample that all surfaces to which the product was exposed were free of contaminating microorganisms. The simulated sample shall be prepared by rinsing the filling equipment with sterile 1.0 percent peptone solution, pH 7.1 ± 0.1, which shall be discharged into a final container by the same method used for filling the final container with the product.

(7) *Samples—large volume of product in final containers.* For Normal Serum Albumin (Human), Plasma Protein Fraction (Human), and Fibrinogen (Human) when the volume of product in the final container is 50 milliliters or more, the final containers selected as the test sample may contain less than the full volume of product in the final container of the filling from which the sample is taken: *Provided,* That the containers and closures of the sample are identical with those used for the filling to which the test applies, and the sample represents all stages of that filling.

(8) *Diagnostic products not intended for injection.* For diagnostic products not intended for injection, (i) only the Thioglycollate Medium test incubated at 30° to 32° C. is required, (ii) the volume of material for the bulk test shall be no less than 2.0 mil., and (iii) the sample for the final container test shall be no less than three final containers if the total number filled is 100 or less, and, if greater, one additional container for each additional 50 containers or fraction thereof, but the sample need be no more than 10 containers.

(9) *Immune globulin preparations. For immune globulin preparations, the test samples from the bulk material and from each final container need be no more than 2.0 ml.*

[38 FR 32056, Nov. 20, 1973, as amended at 41 FR 4015, Jan. 28, 1976; 41 FR 10428, Mar. 11, 1976; 43 FR 10558, Mar. 14, 1978; 43 FR 47182, Oct. 13, 1978; 44 FR 11754, Mar. 2, 1979]

§610.13 Purity.

Products shall be free from extraneous material except for unavailable bacteriophage. In addition, products shall be tested as provided in paragraphs (a) and (b) of this section.

(a) *Test for residual moisture.* Each lot of dried product shall be tested for residual moisture and other volatile substances.

(1) *Procedure.* The test for dried products shall consist of measuring the maximum loss of weight in a weighed sample equilibrated over anhydrous PO at a pressure of not more than 1 mm. of mercury, and at a temperature of 20° to 30° C. for as long as it has been established is sufficient to result in a constant weight.

(2) *Test results; standard to be met.* The residual moisture and other volatile substances shall not exceed 1 percent except that, (i) they shall not exceed 1.5 percent for BCG Vaccine; (ii) they shall not exceed 2 percent for Measles Virus Vaccine, Live, Attenuated; Measles-Smallpox Vaccine, Live; Rubella Virus Vaccine, Live; and Antihemophilic Factor (Human); (iii) they shall not exceed 3 percent for Modified Plasma (Bovine); Thrombin; Fibrinogen; Streptokinase; and Streptokinase-Streptodornase; and (iv) they shall not exceed 4.5 percent for Antibody to Hepatitis B Surface Antigen for the Reversed Passive Hemagglutination Test.

(b) *Test for pyrogenic substances.* Each lot of any product intended for use by injection shall be tested for pyrogenic substances by intravenous injection into rabbits as provided in paragraph (b)(1) and (2) of this

section: *Provided,* That notwithstanding any other provision of Subchapter F of this chapter, the test for pyrogenic substances is not required for the following products: Products containing formed blood elements; Cryoprecipitated Antihemophilic Factor (Human); Single Donor Plasma (Human); Source Plasma (Human); Normal Horse Serum; bacterial, viral, and rickettsial vaccines and antigens; toxoids; toxins; allergenic extracts; venoms; diagnostic substances and trivalent organic arsenicals.

(1) *Test dose.* The test dose for each rabbit shall be at least 3 milliliters per kilogram of body weight of the rabbit and also shall be at least equivalent proportionately, on a body weight basis, to the maximum single human dose recommended, but need not exceed 10 milliliters per kilogram of body weight of the rabbit, except that: (i) Regardless of the human dose recommended, the test dose per kilogram of body weight of each rabbit shall be at least 1 milliliter for immune globulins derived from human blood and at least 30 milligrams for Fibrinogen (Human); (ii) for Streptokinase, Streptokinase-Streptodornase, Aggregated Radio-Iodinated (I^{131}) Albumin (Human), Radio-Chromated (Cr^{31}) Serum Albumin (Human), Radio-Iodinated (I^{135}) Serum Albumin (Human), and Radio-Iodinated (I^{131})Serum Albumin (Human), the test dose shall be at least equivalent proportionately, on a body weight basis, to the maximum single human dose recommended.

(2) *Procedure; test results; standards to be met.* Use only overtly healthy mature rabbits. House the rabbits individually in an area of uniform temperature (±3° C), free from disturbances likely to excite them. Rabbits for pyrogen tests may not be used within 2 weeks following their having been given a test sample that was adjudged pyrogenic, and in no case may a rabbit be used more frequently than every 48 hours. Before using a rabbit that has never been used in a pyrogen test, condition it by a sham test that includes all the steps prescribed in

paragraph (b)(2) of this section, except injection of the test dose. Perform the test under environmental conditions similar to those under which the rabbits are housed. During the test withhold all food, except water, from the rabbits. Determine the control temperature of each rabbit not more than 40 minutes before injecting the test dose. The control temperature is determined by inserting the temperature measuring device into the rectum of the test rabbit to a depth of not less than 7.5 centimeters and allowing sufficient time to reach a maximum temperature before taking the reading. The control temperature recorded for each rabbit constitutes the temperature from which any subsequent rise following the injection of the material is calculated. If the rectal temperature measuring device is to remain inserted throughout the testing period, restrain the rabbits in a manner that will allow them to assume a natural resting position. In any one test, use only those rabbits whose control temperatures do not deviate more than 1° C from each other, and do not use any rabbits with a temperature exceeding 39.8° C. Warm the test product to approximately 37° C, and inject the test dose into an ear vein of each of the three rabbits. Injection of each test dose shall be completed within 10 minutes after the start of administration. Record the temperature of each rabbit at 1, 2, and 3 hours subsequent to the starting time of each injection. The lot meets the requirements for absence of pyrogens if no rabbit shows a rise in temperature of 0.6° C or more above its respective control temperature at any time period, and if the sum of the three rabbits' individual maximum temperature rises does not exceed 1.4° C.

(3) *Retest.* If the lot fails to meet the test requirements prescribed in paragraph (b)(2) of this section, the test may be repeated once using five other rabbits. The temperature rises recorded for all eight rabbits used in testing shall be included in determining whether the requirements are met. The lot meets the requirements

ANTIGENS

Cholera Vaccine, Inaba serotype.
Cholera Vaccine, Ogawa serotype.
Diphtheria Toxin for Schick Test.
Pertussis Vaccine.
Tuberculin, Old.
Tuberculin, Purified Protein Derivative.
Typhoid Vaccine.

BLOOD DERIVATIVE

Thrombin.

(b) *Opacity standard.* The U.S. Opacity Standard shall be applied in estimating the bacterial concentration of all bacterial vaccines. The assigned value of the standard when observed visually is 10 units. The assigned value of the standard when observed with a photometer is (1) 10 units when the wavelength of the filter is 530 millimicrons, (2) 10.6 units when the wavelengths of the filter is 650 millimicrons, and (3) 9 units when the wavelength of the filter is 420 millimicrons.

[38 FR 32056, Nov. 20, 1973, as amended at 41 FR 10429, Mar. 11, 1976; 41 FR 18295, May 3, 1976]

§610.21 Limits of potency.

The potency of the following products shall be not less than that set forth below and products dispensed in the dried state shall represent liquid products having the stated limitations.

ANTIBODIES

Diphtheria Antitoxin, 500 units per milliliter.
Tetanus Antitoxin, 400 units per milliliter.
Tetanus Immune Globulin (Human), 50 units of tetanus antitoxin per milliliter.

ANTIGENS

Cholera Vaccine, 8 units each of Inaba and Ogawa serotype antigens per milliliter.

Pertussis Vaccine, 12 units per total human immunizing dose.

Typhoid Vaccine, 8 units per milliliter.

[41 FR 10429, Mar. 11, 1976, as amended at 41 FR 18295, May 3, 1976]

Subpart F—Dating Period Limitations

§610.50 Date of manufacture.

The date of manufacture shall be determined as follows:

(a) For products for which an official standard of potency is prescribed in either §610.20 or §610.21, or which are subject to official potency tests, the date of initiation by the manufacturer of the last valid potency test.

(b) For products that are not subject to official potency tests, (1) the date of removal from animals, (2) the date of extraction, (3) the date of solution, (4) the date of cessation of growth, or (5) the date of final sterile filtration of a bulk solution, whichever is applicable.

[38 FR 32056, Nov. 20, 1973, as amended at 42 FR 27582, May 31, 1977]

§610.51 Periods of cold storage.

Except as otherwise provided in the regulations of this subchapter, products may be held in cold storage by the manufacturer as follows:

At a temperature not above 5° C.—1 year.
At a temperature not above 0° C.—2 years.

shall remain uncovered for its full length or circumference to permit inspection of the contents.

§610.61 Package label.

The following items shall appear on the label affixed to each package containing a product:

(a) The proper name of the product;

(b) The name, address, and license number of manufacturer;

(c) The lot number or other lot identification;

(d) The expiration date;

(e) The preservative used and its concentration, or if no preservative is used and the absence of a preservative is a safety factor, the words "no preservative";

(f) The number of containers, if more than one;

(g) The amount of product in the container expressed as (1) the number of doses, (2) volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable;

(h) The recommended storage temperature;

(i) The words "Shake Well", "Do Not Freeze" or the equivalent, as well as other instructions, when indicated by the character of the product;

(j) The recommended individual dose if the enclosed container(s) is a multiple-dose container,

(k) The route of administration recommended, or reference to such directions in an enclosed circular;

(l) Known sensitizing substances, or reference to an enclosed circular containing appropriate information;

(m) The type and calculated amount of antibiotics added during manufacture;

(n) The inactive ingredients when a safety factor, or reference to an enclosed circular containing appropriate information;

(o) The adjuvant, if present;

(p) The source of the product when a factor in safe administration;

(q) The identity of each microorganism used in manufacture, and where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information;

(r) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words "No U.S. standard of potency."

(s) For injectible products prepared from human blood, plasma or serum, a statement that the product was prepared from blood that was nonreactive when tested for hepatitis B surface antigen. In lieu of inclusion on the package label, such information may be included in a circular enclosed with the package.

[38 FR 32056, Nov. 20, 1973, as amended at 40 FR 29711, July 15, 1975]

§610.62 Proper name; package label; legible type.

(a) *Position.* The proper name of the product on the package label shall be placed above any trademark or trade name identifying the product and symmetrically arranged with respect to other printing on the label.

(b) *Prominence.* The point size and typeface of the proper name shall be at least as prominent as the point size and typeface used in designating the trademark and trade name. The contrast in color value between the proper name and the background shall be at least as great as the color value between the trademark and trade name and the background. Typography, layout, contrast, and other printing features shall not be used in a manner that will affect adversely the prominence of the proper name.

(c) *Legible type.* All items required to be on the container label and package label shall be in legible type. "Legible type" is type of a size and character which can

for absence of pyrogens if not more than three of the eight rabbits show individual rises in temperature of 0.6° C or more, and if the sum of the eight individual maximum temperature rises does not exceed 3.7° C.

(c) *Different tests equal or superior.* A different test for residual moisture may be performed provided that prior to its performance the manufacturer submits data which the Commissioner of Food and Drugs finds adequate to establish that the different test is equal or superior to the test described in paragraph (a) of this section and makes the finding a matter of official record.

[38 FR 32056, Nov. 20, 1973, as amended at 40 FR 29710, July 15, 1975; 41 FR 10429, Mar. 11, 1976; 41 FR 41424, Sept. 22, 1976]

§610.14 Identity.

The contents of a final container of each filling of each lot shall be tested for identity after all labeling operations shall have been completed. The identity test shall be specific for each product in a manner that will adequately identify it as the product designated on final container and package labels and circulars, and distinguish it from any other product being processed in the same laboratory. Identity may be established either through the physical or chemical characteristics of the product, inspection by macroscopic or microscopic methods, specific cultural tests, or in vitro or in vivo immunological tests.

§610.15 Constituent materials.

(a) *Ingredients, preservative, diluents, adjuvants.* All ingredients used in a licensed product, and any diluent provided as an aid in the administration of the product, shall meet generally accepted standards of purity and quality. Any preservative used shall be sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the

recipient, and in the combination used shall not denature the specific substances in the product below the minimum acceptable potency within the dating period when stored at the recommended temperature. Products in multiple dose containers shall contain a preservative, except that a preservative need not be added to Yellow Fever Vaccine, Poliovirus Vaccine, Live, Oral, or to viral vaccines labeled for use with the jet injector, or to dried vaccines when the accompanying diluent contains a preservative. An adjuvant shall not be introduced into a product unless there is satisfactory evidence that it does not affect adversely the safety or potency of the product. In no event shall the recommended individual dose of a biological product contain more than 0.85 milligram of aluminum, determined by assay, or more than 1.14 milligrams of aluminum, determined by calculation on the basis of the amount of aluminum compound added.

(b) *Extraneous protein; cell culture produced vaccines.* Extraneous protein known to be capable of producing allergenic effects in human subjects shall not be added to a final virus medium of cell culture produced vaccines intended for injection. If serum is used at any stage, its calculated concentration in the final medium shall not exceed 1:1,000,000.

(c) *Antibiotics.* A minimum concentration of antibiotics, other than penicillin, may be added to the production substrate of viral vaccines.

§610.16 Total solids in serums.

Except as otherwise provided by regulation, no liquid serum or antitoxin shall contain more than 20 percent total solids.

§610.17 Permissible combinations.

Licensed products may not be combined with other licensed products either therapeutic, prophylactic or

diagnostic, except as a license is obtained for the combined product. Licensed products may not be combined with nonlicensable therapeutic, prophylactic, or diagnostic substances except as a license is obtained for such combination.

§610.18 Cultures.

(a) *Storage and maintenance.* Cultures used in the manufacture of products shall be stored in a secure and orderly manner, at a temperature and by a method that will retain the initial characteristics of the organisms and insure freedom from contamination and deterioration.

(b) *Identity and verification.* Each culture shall be clearly identified as to source strain. A complete identification of the strain shall be made for each new stock culture preparation. Primary and subsequent seed lots shall be identified by lot number and date of preparation. Periodic tests shall be performed as often as necessary to verify the integrity of the strain characteristics and freedom from extraneous organisms. Results of all periodic tests for verification of cultures and determination of freedom from extraneous organisms shall be recorded and retained.

§610.19 Status of specific products; Group A streptococcus.

The presence of Group A streptococcus organisms and derivatives of Group A streptococcus in Bacterial Vaccines and Bacterial Antigens with "No U.S. Standard of Potency" may induce dangerous tissue reactions in humans. Available data demonstrate that they are unsafe as ingredients in products for human use. Group A streptococcus organisms and derivatives of Group A streptococcus are prohibited from Bacterial Vaccines and Bacterial Antigens with "No U.S. Standard of Potency." Any Bacterial Vaccine or Bacterial Antigen with

"No U.S. Standard of Potency" containing Group A streptococcus organisms or derivatives of Group A streptococcus in interstate commerce is in violation of section 351 of the Public Health Service Act (42 U.S.C. 262).

(Secs. 201, 502, 505, 701, 52 Stat. 1040-1042 as amended, 1050-1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371); sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262); secs. 4, 10, 60 Stat. 238 and 242 as amended (5 U.S.C. 553, 702, 703, 704))
[44 FR 1549, Jan. 5, 1979]

Subpart C—Standard Preparations and Limits of Potency

§610.20 Standard preparations.

Standard preparations made available by the Bureau of Biologics shall be applied in testing, as follows:

(a) *Potency standards.* Potency standards shall be applied in testing for potency all forms of the following:

ANTIBODIES

Botulism Antitoxin, Type A.
Botulism Antitoxin, Type B.
Botulism Antitoxin, Type E.
Diphtheria Antitoxin.
Histolyticus Antitoxin.
Oedematiens Antitoxin.
Perfringens Antitoxin.
Antipertussis Serum.
Antirabies Serum.
Sordellii Antitoxin.
Staphylococcus Antitoxin.
Tetanus Antitoxin.
Vibrion Septique Antitoxin.

§610.52 Dating period.

The dating period for a combination of two or more products shall be no longer than the dating period of the component product with the shortest dating period. The dating period for a product shall begin on the date of manufacture, except that the dating period may begin on the date of issue from the manufacturer's cold storage, provided the product was maintained as prescribed in §610.51. If held in the manufacturer's cold storage beyond the period prescribed, the dating period shall be reduced by a corresponding period.

§610.53 Dating periods for specific products.

(a) *General.* The following dating periods are based on data relating to usage, clinical experience or laboratory tests that establish the period beyond which the product cannot be expected beyond reasonable doubt to yield its specific results and retain its safety, purity, and potency, provided the product is maintained at the recommended temperatures. The standards prescribed by the regulations in this subchapter, designed to insure continued safety, purity, and potency of the products, are based on the dating periods set forth below, Cold storage periods and temperatures prescribed in §610.51 shall apply and outside labels shall recommend storage between 2° C. and 8° C., except when specifically provided otherwise. (Storage temperatures and storage periods are given in parentheses after the dating periods below when they differ from those specified in §610.51.)

[Table Omitted]

(b) *Exemptions.* Exemptions or modifications shall be made only upon written approval, in the form of an amendment of the product license, issued by the Director, Bureau of Biologics.

[38 FR 32056. Nov. 20, 1973, as amended at 39 FR 9660, Mar. 13, 1974; 39 FR 20371, June 10, 1974; 39 FR 27796, Aug. 1, 1974; 40 FR 4304, Jan. 29. 1975; 40

FR 29711, July 15, 1975; 41 FR 10768, Mar. 12, 1976; 41 FR 40101, Sept. 17, 1976; 42 FR 14095, Mar. 15, 1977; 42 FR 54541, Oct. 7, 1977; 42 FR 59878, Nov. 22, 1977; 43 FR 4007, Jan. 31, 1978; 43 FR 10558, Mar. 14, 1978; 43 FR 34459, Aug. 4, 1978]

Subpart G—Labelling Standards

§610.60 Container label.

(a) *Full label.* The following items shall appear on the label affixed to each container of a product capable of bearing a full label:

(1) The proper name of the product;

(2) The name, address, and license number of manufacturer;

(3) The lot number or other lot identification;

(4) The expiration date;

(5) The recommended individual dose, for multiple dose containers.

(b) *Package label information.* If the container is not enclosed in a package, all the items required for a package label shall appear on the container label.

(c) *Partial label.* If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label.

(d) *No container label.* If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label.

(e) *Visual inspection.* When the label has been affixed to the container a sufficient area of the container

be read with ease when held in a good light and with normal vision.

§610.63 Divided manufacturing responsibility to be shown.

If two or more establishments participate in the manufacture of a product, the name, address, and license number of each must appear on the package label, and on the label of the container if capable of bearing a full label.

§610.64 Name of selling agent or distributor.

The name and address of the selling agent or distributor of a product may appear on the label under the designation of "selling agent" or "distributor" provided that the name and address of the manufacturer is given precedence in prominence.

§610.65 Products for export.

Labels on packages or containers of products for export may be adapted to meet specific requirements of the regulations of the country to which the product is to be exported provided that in all such cases the minimum label requirements prescribed in §610.60 are observed.

PART 620—ADDITIONAL STANDARDS FOR BACTERIAL PRODUCTS

Subpart A—Pertussis Vaccine

Sec.

620.1 Pertussis Vaccine.
620.2 Production.
620.3 U.S. Standard preparations.
620.4 Potency test.
620.5 Mouse toxicity test.
620.6 General requirements.
620.7 Equivalent methods.

CROSS REFERENCES: For U.S. Customs Service regulations relating to viruses, serums, and toxins, see 19 CFR 12.21-12.23. For U.S. Postal Service regulations relating to the admissibility to the United States mails see Parts 124 and 125 of the Postal Service Manual, that is incorporated by reference in 39 CFR Part 111.

Subpart A—Pertussis Vaccine

§620.1 Pertussis Vaccine.

The proper name of this product shall be "Pertussis Vaccine", which shall be an aqueous preparation of either killed whole *Bordetella pertussis* bacteria or a fraction of *Bordetella pertussis* bacteria. The vaccine may be precipitated or absorbed and may be combined with other antigens.

§620.2 Production.

(a) *Propagation of bacteria.* Human blood shall not be used in culture medium for propagating bacteria either for seed or for vaccine. The culture medium for propagating bacteria for vaccine shall not contain ingredients known to be capable of producing allergenic effects in human subjects, except blood or blood products from lower animals other than the horse. When blood or a blood product is used, it shall be removed by washing the harvested bacteria. The bacterial concentrate shall be free of extraneous bacteria, fungi, and yeasts, as demonstrated by microscopic examination and cultural methods.

(b) *Bacterial content.* (1) The opacity of the bacterial concentrate shall be determined in terms of the U.S. Opacity Standard not later than 2 weeks after the harvest of the bacteria and before any treatment capable of altering the opacity of the bacterial concentrate.

(2) The total immunizing dose of a vaccine prepared with whole bacteria shall contain (i) in the case of

nonadsorbed vaccine no more bacteria than the equivalent of 60 opacity units and (ii) in the case of adsorbed vaccine no more than the equivalent of 48 opacity units.

(c) *Detoxification.* After removing a sample for purity testing, the bacteria shall be killed and detoxified either (1) by heating, (2) by addition of a chemical agent and appropriate aging, or (3) by any combination of the stated procedures. The procedure used shall be one that has been shown to have no adverse effect on required safety, purity, and potency.

(d) *Preservative.* The vaccine shall contain a preservative.

§620.3 U.S. Standard preparations.

(a) The U.S. Standard Pertussis Vaccine shall be used for determining the potency of Pertussis Vaccine.

(b) The U.S. Opacity Standard shall be used in estimating the bacterial content of the vaccine and of the challenge culture.

§620.4 Potency test.

The number of protective units of the total human immunizing dose shall be estimated for each lot of vaccine from the results of simultaneous intracerebral mouse protection tests of the vaccine under test and the U.S. Standard Pertussis Vaccine. The potency test shall be performed as follows:

(a) *Mice.* Healthy mice shall be used, all from a single strain and of the same sex, or an equal number of each sex in each group, with individual weight varying no more than 4 grams in a single test. In no event shall any of the mice weigh less than 10 grams or more than 20 grams. A system of randomization shall be used to distribute the mice into the groups, with respect to shelf position and to determine the order of challenge. There shall be at least 3 groups consisting of no less than 16 mice each, for each vaccine. In addition, there shall be at

least 4 groups consisting of no less than 10 mice each, for control purposes: one group for the challenge dose and 3 groups for titrating the virulence of the challenge dose.

(b) *Vaccination.* (1) Five-fold serial dilutions of the vaccine to be tested and of the standard vaccine shall be made in 0.85 percent sodium chloride solution. The dilutions of the vaccine under test shall have the same protective unitage, based on an estimate of 12 units per total human immunizing dose, as the unitage of the corresponding dilution of the standard vaccine.

Each mouse in each group for vaccination shall be injected intraperitoneally with 0.5 ml. of the appropriate dilution.

(2) the interval between vaccination and challenge shall be 14 to 17 days. At least 87.5 percent of the mice in each group shall survive the period between vaccination and challenge and each mouse challenged shall appear healthy.

(c) *The challenge.* (1) The challenge culture of *Bordetella pertussis* for each test shall be taken from a batch of cultures which have been maintained by a method, such as freeze-drying, that retains constancy of virulence.

(2) The challenge and virulence titration doses shall be prepared as follows: The bacteria shall be harvested from a 20 to 24 hour culture grown on Bordet-Gengou medium seeded from a rapidly growing culture less than 48 hours old and uniformly suspended in a solution containing 1.0 percent casein peptone and about 0.6 percent sodium chloride at pH 7.1 ± 0.1. The suspension, freed from agar particles and clumps of bacteria, and adjusted to an opacity of 10 units, shall be diluted in the solution used for suspending the bacteria, to provide in a volume of 0.03 ml. (i) a challenge dose of

0.0001 opacity units (1:3000) and (ii) virulence titration doses of 1/50, 1/250 and 1/1250 respectively of the challenge dose.

(3) Each vaccinated mouse shall be injected intracerebrally with the challenge dose. The four groups of control mice shall be injected intracerebrally with the challenge dose and its three dilutions, respectively. The challenge-dose control mice shall be injected last. The interval between the removal of the bacteria from the culture medium and the injection of the last mouse shall not exceed 2½ hours.

(d) *Recording the results.* The mice shall be observed for 14 days. Mice dying within 72 hours after challenge shall be excluded from the test. Records shall be maintained of the number of mice that die after 72 hours and of the number of mice showing both paralysis and enlargement of the head at the end of 14 days. All mice that show both paralysis and enlargement of the head shall be considered as deaths for the purposes of determining the ED_{50}.

(e) *Validity of the test.* The test shall be valid provided (1) the ED_{50} of the vaccine under test and the standard vaccine is between the largest and smallest vaccinating doses; (2) the limits of one standard deviation of each ED_{50} fall within the range of 64 percent to 156 percent; (3) the protective response is graded in relation to the vaccinating doses; (4) the dose-response curves of the vaccine under test and the standard vaccine are parallel; (5) the challenge dose contains approximately 200 LD_{50}; (6) the LD_{50} contains no more than 300 colony forming units; and (7) the 1/1250 dilution of the challenge dose contains no less than 10 and no more than 50 colony forming units.

(f) *Estimate of the potency.* The ED_{50} of each vaccine shall be calculated by a method that provides an estimate of the standard deviation. The protective unit value per total human immunizing dose of the vaccine

under test shall be calculated in terms of the unit value of the standard vaccine.

(g) *Potency requirements.* The vaccine shall have a potency of 12 units per total human immunizing dose based upon either a single test estimate of no less than 8 units or a two-, three- or four-test geometric mean estimate of no less than 9.6, 10.8, or 12 units, respectively, except that for the vaccine in a multiple antigen product containing Poliomyelitis Vaccine, the estimate shall be no less than 14 units. In no event shall the estimate be more than 36 units.

(h) *Test design variation.* Variations in the design of the potency test may be permitted providing the results are demonstrated to be of equal or greater precision.

§620.5 Mouse toxicity test.

The final vaccine shall be demonstrated to be free from toxicity by the following test:

A group of no less than 10 mice, each mouse weighing 14 to 16 grams, shall have free access to food and water for no less than 2 hours before injection. The group weight of the mice shall be determined immediately prior to injection. Each mouse shall be injected intraperitoneally with a test dose of one-half of the largest recommended single human dose of the final vaccine in a volume of no less than 0.5 ml. nor more than 0.75 ml. The group weight of the mice shall be determined at the end of 72 hours and at the end of 7 days after injection. At the end of 72 hours the average weight per mouse may be no less than the average weight per mouse immediately preceding the injection; at the end of 7 days the average weight gain per mouse may be no less than 3.0 grams; and at the end of 7 days there may be vaccine-related deaths of no more than 5 percent of the total number of mice in all the toxicity tests performed.

§620.6 General requirements.

(a) *Safety.* Each lot of product containing Pertussis Vaccine shall be tested for safety by the procedures prescribed in §610.11 of this chapter except that the test shall consist of the intraperitoneal injection of no less than one-half of the recommended largest individual human dose into each of the mice, and either the intraperitoneal injection of no less than three times the recommended largest individual human dose, or the subcutaneous injection of 5.0 milliliters into each of the guinea pigs.

(b) *Dose.* These additional standards are based on a single injection of 0.5 ml., 1.0 ml., or 1.5 ml., and a total human immunizing dose of three single injections of a nonadsorbed vaccine, and two or three single injections of an adsorbed vaccine.

(c) *Product characteristics.* Recommendations shall be made through appropriate labeling that the product after issue should not be frozen and should be well shaken immediately prior to use.

(d) *Labeling.* In addition to the items required by other applicable labeling provisions of this part, the package label shall give the following information:

1. For a vaccine containing a precipitant or an adsorbent, the word "Adsorbed" shall follow the proper name in the same style of type and prominence as the proper name.

2. The total immunizing dose contains 12 units of pertussis vaccine.

(e) *Multiple antigen products.* The Pertussis Vaccine components of multiple antigen products shall be manufactured pursuant to these additional standards, except that the mouse toxicity test (§620.5) and the potency test (§620.4) shall be performed on the multiple antigen product.

(f) *Adsorbed vaccines.* Only aluminum compound reagents shall be introduced into the product to cause

precipitation or adsorption of either Pertussis Vaccine or other antigens incorporated with Pertussis Vaccine.

(g) *Freezing prohibition.* Pertussis Vaccine and multiple antigen products of which Pertussis Vaccine is a component shall not be frozen at any time during storage.

(h) *Samples and protocols.* For each lot of vaccine, the following material shall be submitted to the Director, Bureau of Biologics, Food and Drug Administration, Building 29A, 9000 Rockville Pike, Bethesda, MD 20205.

(1) A sample of no less than 20 milliliters of the final product for pertussis vaccine testing.

(2) Protocols showing summaries of the manufacturing processes and the results of all mouse toxicity (§620.5) and potency (§620.4) tests performed.

[38 FR 32064, Nov. 20, 1973, as amended at 41 FR 10891, Mar. 15, 1976; 41 FR 35480, Aug. 23, 1976]

§620.7 Equivalent methods.

Modification of any particular manufacturing method or process or the conditions under which it is conducted as set forth in the additional standards relating to Pertussis Vaccine shall be permitted whenever the manufacturer presents evidence that demonstrates the modification will provide assurances of the safety, purity, and potency of the vaccine that are equal to or greater than the assurances provided by such standards, and the Commissioner of Food and Drugs so finds and makes such finding a matter of official record.

APPENDIX G

Sixth International Symposium on Pertussis

Jack Masur Auditorium
Warren Grant Magnuson Clinical Center
National Institutes of Health
Bethesda, Maryland
September 26-28, 1990

PRELIMINARY PROGRAM

September 26

9:00 **Opening Ceremonies**
9:30 **Virulence factors of *Bordetella pertussis:* structure and function**
Co-chairpersons: Drusilla L. Burns
William E. Goldman
9:30 **Introduction**
9:35 **Tracheal cytotoxin of *Bordetella pertussis*: biosynthesis, structure and specificity.** W.E. Goldman, J.L. Collier, B.T. Cookson, G.R. Marshall, K.M. Erwin.
9:55 Discussion
10:00 **Structural and functional consequences of the interaction of calcium with adenylate cyclase toxin from *Bordetella pertussis*.** Erik L. Hewlett, Lloyd Gray, Ingrid Ehrmann, Peter Fremgen, Margaretta Allieta, Mary Gray.
10:20 Discussion
10:25 ***Bordetella pertussis* adenylate cyclase is a bifunctional toxin: structure and mode of interaction with host cells.** Emanuel Hanski, Arie Rogel.
10:45 Discussion
10:50 Coffee Break
11:20 **Effect of exogenous agents on the action of *Bordetella* heat-labile toxin.** Masahiko Endoh, Masaaki Nagai, Drusilla L. Burns, Yasukiyo Nakase, Charles R. Manclark.
11:40 Discussion
11:45 **Construction of a genetically detoxified pertussis toxin.** Rino Rappuoli, Mariagrazia Pizza, Luciano Nencioni, Audino Podda.
12:05 Discussion
12:10 **Molecular biological studies on the structure-function**

relationship of pertussis toxin and filamentous hemagglutinin. Camille Locht, Teresa Cabezon.

12:30 Discussion

12:35 **Studies on the entry of pertussis toxin into CHO cells.** Sally Z. Hausman, Charles R. Manclark, Drusilla L. Burns.

12:50 Discussion

12:55 Adjourn

Lunch

2:30 **Characterization of mRNA and *in vitro* mutagenesis of Goa, the 39 kDa pertussis toxin substrate.** Mikako Tsuchiya, Joel Avigan, Kenneth B. Newman, James J. Murtagh, Jr., Linda A. Stevens, Mary W. Walker, Su-Chen Tsai, Inex M. Serventi, S. Russ Price, C. William Angus, Joel Moss, Martha Vaughan.

2:45 Discussion

2:50 **Elucidation of linear B-cell epitopes in the pertussis toxin S3 subunit by anti-peptide antibodies.** Jutta Marzillier, Barbel Raupach, Miroslav Szulczynski, M. Alexander Schmidt.

3:05 Discussion

3:10 **Purification, characterization and immunological evaluation of the 69kDa outer membrane protein of *Bordetella pertussis*.** C. Caplau, E. Simoen, D. Plainchamps, M. Comberbach, P. Roelants, P. Desmons, Ph. Permanne. J. Petre.

3:25 Discussion

3:30 Adjourn

3:30 **Poster Session**

Co-Chairpersons: Michael J. Brennan
Elizabeth Leininger

6:30 Adjourn Poster Session

September 27

9:00 **Surface proteins of *Bordetella pertussis:* their role as bacterial adhesins and protective antigens.**
Co-chairpersons: Michael J. Brennan
James L. Cowell

9:00 **Introduction**

9:05 **Recognition of a eukaryotic integrin by a bacterial adhesin: *Bordetella pertussis* filamentous hemagglutinin binds CR3 on human macrophages.** David A. Relman, Elaine Tuomanen, Stanley Falkow, Douglas T. Golenbock, Kirsi Saukkonen, Samuel D. Wright.

9:25 Discussion

9:30 **Surface proteins of *Bordetella pertussis:* role in adherence.** Elizabeth Leininger, James G. Kenimer, Michael J. Brennan.

9:50 Discussion

9:55 **Mechanism of *Bordetella pertussis* invasion of HeLa 229 cells.** Carol A. Ewanowich, Elizabeth Leininger, James G. Kenimer, Mark S. Peppler.

10:15 Discussion

10:20 **Mutations in the *bug* locus and their effects on *Bordetella pertussis* invasion of HeLa 229 cells.** Cynthia K. Lee, Angela L. Roberts, Theresa M. Finn, Stefan Knapp, John J. Mekalanos.

10:40 Discussion

10:45 Coffee Break

11:15 **Structure-function studies of *Bordetella pertussis* fimbriae.** A. Robinson, L.I.Irons, R.N. Seabrook, A. Pearce, M. Matheson, S.G.P. Funnell.

11:35 Discussion

11:40 **Identification of an immunodominant region of the protective protein P.69 from *Bordetella pertussis.*** I.G. Charles, Li J. Li, G. Dougan, D.J. Pickard, M.J. Brennan, C.R. Manclark, M.Au Jensen, I. Heron, P. Novotny, N.F. Fairweather.

12:00 Discussion

12:05 **Characterization of the major outer membrane porin protein of *Bordetella pertussis.*** Julie H. Hannah, Martin Kessel, Zhong Ming Li, Alasdair C. Steven, Nga Y. Nguyen, John B. Ewell, Charles R. Manclark, Michael J. Brennan.

12:25 Discussion

12:30 **Outer membrane vesicles of *Bordetella pertussis* are protective antigens in the mouse intracerebral challenge model.** Jan T. Poolman, Ann K. Barlow, Hendrick-Jan Hamstra, Betsy Kuipers, Henk Loggen, Jaap Nagel.

12:50 Discussion

12:55 Adjourn

Lunch

2:30 **Immunology and host-parasite interactions of *Bordetella pertussis*.**

Co-chairpersons: M. Teresa De Magistris
Roberta D. Shahin

2:30 **Introduction**

2:35 **T-Cell immunity against pertussis toxin in adult volunteers immunized with PT-9K/129G.** Maria Teresa De Magistris, Annallsa Di Tommaso, Paola Bossu, Sandra Nuti, Claudia Winzler, Rino Rappuoli, Aldo Tagliabue.

2.55 Discussion

3:00 **T-Cell response to *Bordetella pertussis* antigens in aerosol infected mice.** K.H.G. Mills, A. Barnard, K. Redhead.

3:20 Discussion

3:25 **Cell-modiated immune response in patients with pertussis and in asymptomatic exposed contacts.** Dean A. Blumberg, Evelyn Pineda, Linda P. Smith, Patricia Chatfield, Chris Anna M. Mink, Peter D. Christenson, James D. Cherry.

3:40 Discussion

3:45 **IgE response to *Bordetella pertussis* filamentous hemagglutinin and pertussis toxin in mice.** Diane S. J. Lindsay, Roger Parton, Alastair C. Wardlaw.

3:55 Discussion

4:00 **IgE antibodies to pertussis toxin in children immunized with an acellular pertussis vaccine (JNIH-6).** Margareta Blennow, Marta Granström, Bengt Björksten.

4:10 Discussion

4:15 Coffee Break

4:45 **Live oral attenuated *Salmonella typhimurium* vaccine vectors which induce formation of antibody to *Bordetella pertussis*.** Charlotte Parker, Christine Molina, Sandra M. Kelly, Roy Curtiss III, Jinan Yu.

5:00 Discussion

5:05 **Analysis of protective mucosal immunity to respiratory *Bordetella pertussis* infection.** Roberta D. Shahin, Diana F. Amsbaugh, Mayumi Endoh, Charles R. Manclark.

5:25 Discussion

5:30 **Adenylate cyclase toxin is critical for bacterial colonization by *Bordetella pertussis* and pertussis toxin is critical for the lethal infection in infant mice.** Tina St. Mary Goodwin, Alison Ann Weiss.
5:45 Discussion
5:50 ***Bordetella pertussis* adenylate cyclase: a protective antigen against colonization and lethality in murine respiratory and intracerebral models.** Nicole Guiso, Marek Szatanik, Murielle Rocancourt.
6:05 Discussion
6:10 Adjourn
Hyatt Regency Hotel, Bethesda
6:30 Cash Bar
7:30 Dinner –

September 28

9:00 **Molecular genetics and regulation of virulence factors.**
Co-chairpersons: Camille Lochi
E. Scott Stibitz

9:00 **Introduction**

9:05 **Molecular and genetic analysis of the *Bordetella pertussis bug* regulon.** Craig R. Roy, Jeff F. Miller, Stanley Falkow.

9:25 Discussion

9:30 **Cellular localization of proteins encoded by the *vir* locus of *Bordetella pertussis*.** S. Stibitz, M.-S. Yang.

9:50 Discussion

9:55 **Expression, regulation and secretion of the adenylate cyclase-hemolysin bifunctional protein.** O. Barzu, J. Bellalou, A. Danchin, A.-M. Gilles, P. Glaser, S. Goyard, D. Ladant. B.M. Laoide, H. Munier, H. Sakamoto, A. Ullman.

10:15 Discussion

10:20 **A strategy for studying pathogenic mechanisms: transposon insertion mutations with conditional phenotypes.** B.T. Cookson, T. Tomcsanyi, D.E. Berg, W.E. Goldman.

10:40 Discussion

10:45 Coffee Break

11:15 ***Bordetella pertussis* fimbriae: role in pathogenesis and mechanism of phase variation.** Frits R. Mooi, Han G.J. van der Heide, Rob Willems, Annet Paul, Henk Brunings, Wim H. Jansen, Piet A.M. Guinee.

11:35 Discussion

11:40 **Identification of a *cya*C gene involved in activation of *Bordetella pertussis* adenylate cyclase toxin.** Eileen M. Barry, Alison A. Weiss, Mary C. Gray, Erik L. Hewlett, Ingrid E. Ehrmann.

11:55 Discussion

12:00 **A sequence upstream of the *cya* operon is required for secretion and phenotypic modulation of the extracellular adenylate cyclase from *Bordetella pertussis*.** K. Saukkonen, S. Sande, H.R. Masure.

12:15 Discussion

12:20 ***Bordetella pertussis* P.69: high level expression, purification and characterization of recombinant P.69 in *E. coli*.** N.F. Fairweather, A.J. Makoff, I.G. Charles, M.D. Oxer, S. Ballantine, M. Roberts, G. Dougan.

12:35 Discussion

12:40 **Autoregulation of the expression of the gene for the pertussis toxin S1 subunit in *Escherichia coli*.** Yves Lobet, Witold Cieplak, Jr.

12:55 Discussion
1:00 Adjourn
Lunch
2:30 **Pertussis epidemiology, diagnosis and clinical studies.**
Co-chairpersons: Bruce D. Meade
C.H. Wirsing von König
2:30 **Introduction**
2:35 **Evaluation of laboratory methods used for the diagnosis of pertussis infection and disease in the Swedish efficacy trial.** J. Storsaeter, H.O. Hallander, C.P. Farrington.
2:55 **Vaccine efficacy for a variety of clinical case definitions.** William C. Blackwelder.
3:05 **New conclusions and lessons learned from the Swedish trial.** P. Olin.
3:20 Discussion
3:30 **Antibody responses, local reactions and systemic symptoms after British whole cell vaccine and three acellular pertussis (DTP) vaccines.** E. Miller, D. L. Miller, L.A.E. Ashworth, P. Waight, K. Harbert.
3:45 Discussion
3:50 **Outstanding issues in the clinical evaluation of acellular pertussis vaccines.** R. Bernier.
4:05 Discussion
4:10 Coffee Break
4:35 **Detection of *Bordetella pertussis* in clinical specimens.** Carl H. Wirsing von König, Jörg E. Hoppe, Angelika Tacken, Horst Finger.
4:55 Discussion
5:00 **Serodiagnosis of pertussis.** B.D. Meade, C.R. Manclark.
5:15 Discussion
5:20 **Nasal IgA responses to pertussis toxin, filamentous hemagglutinin and agglutinogens 2 and 3 induced by *Bordetella pertussis* infection and pertussis vaccination.** M.G. Thomas, L.A.E. Ashworth, E. Miller, H.P. Lambert.
5:35 Discussion
5:40 **Epidemiology of pertussis in Philadelphia.** Sarah S. Long, Margaret C. Fisher, Adamadia Deforest, Joel Mortensen.
6:00 Discussion
6:05 Adjourn
Close – Sixth International Symposium on Pertussis

Sixth International Symposium on Pertussis

POSTER SESSION
PRELIMINARY PROGRAM

Structure-function analysis of the S1 subunit of pertussis toxin using monoclonal antibodies. H. Boux, M. Makinen, S. Cockle, P. Chong, L. Gucciardi, S. Loosmore, M. Klein.

A common structure of the active site of ADP-ribosylating toxins. Mario Domenighini, Cesare Montecucco, Rino Rappuoli.

The enzymatically-active A subunit is required for the leukocytosis-promoting and histamine-sensitizing activities of pertussis toxin. Juan Arciniega, W. Neal Burnette, Timothy D. Bartley, Vernon L. Mar, David W. Whitelely, Charles R. Manclark, Drusilla L. Burns.

Localization of the region of the S1 subunit required for efficient binding of transducin. G. Cortina, J.T. Barbieri.

Protective immunogenicity of synthetic peptides selected from the amino acid sequence of pertussis toxin subunit S1. P. Askelöf, K. Rodmalm, G. Wrangsell, U. Larsson, S.B. Svenson, J. L. Cowell, A. Unden, T. Bartfai.

Structural studies of pertussis toxin. Mary A. Turner, Stella Fawcett, Lindsay Sawyer, Simon van Heyningen.

Preliminary x-ray crystallographic analysis of pertussis toxin. Malini Raghavan, John W. Gotto, Jane V. Scott, Clarence E. Schutt.

The B-oligomer of pertussis toxin: structure function analysis and the delineation of neutralizing epitopes using a panel of monoclonal antibodies. H. Boux, M. Makinen, P. Chong, S. Cockle. G. Zobrist, G. Jackson, S. Loosmore, M. Klein.

Western-blot analysis can fail to detect the predominant neutralizing epitope in pertussis toxin modified by site-directed mutagenesis. Harvey R. Kaslow, John D. Schlotterbeck, Vernon L. Mar, W. Neal Burnette.

Antibody interactions with pertussis toxin. Harvey R. Kaslow, John D. Schlotterbeck, John Gotto.

Mapping of neutralization epitopes on the S2 and S3 subunits of pertussis toxin using synthetic peptides. P. Chong, M. Sydor, E. Wu, G. Zobrist, M. Klein.

Binding properties of pertussis toxin. Maarten H. Witvliet, Hidde L. Ploegh, Peter Hoogerhout, Jan T. Poolman.

Pertussis toxin interacts with immunologically relevant molecules on human lymphocytes. Ruud J. Klapmuts, Dominique J.M. Borsboom, Emmanuel J.H.J. Wietz, Jan Poolman.

The carbohydrate recognition domain mediating binding of pertussis toxin to human cilia and macrophages resides in subunit 2. K. Saukkonen, N. Burnett, V. Mar, E. Tuomanen.

Mouse-protective activities of monoclonal antibodies against pertussis toxin. Hiroko Sato, Yuji Sato.

Modification of the immunological properties of pertussis toxin by chemical inactivation. Luciano Nencioni, Massimo Bugnoli, Daniele Nucci, Samuele Peppoloni, Ilio Marsili, Maria Teresa De Magistris, Rino Rappuoli.

Chemical detoxification studies of pertussis toxin. G. Jackson, P. Chong, L. Tan, R. Fahim, S. Cockle, H. Boux, M. Klein.

Alterations in hepatic drug metabolism following vaccine administration to mice. Sherry Ansher, William Habig.

Evaluation of the effect of pertussis vaccines on the central nervous system by means of the convulsion test with the use of thiosemicarbazide. S. Ya. Kovalskaya, N.A. Ozeretskovsky, N.S. Zakharova.

Effect of pertussis vaccine or pertussigen treatment on the development of type 1, insulin-dependent diabetes mellitus in animal models. Shih-Wen Huang, Roberto Luchetta, Ammon B. Peck.

Isolation and characterization of calmodulin-like protein from *Bordetella pertussis*. M. Nagai, M. Endoh, Y. Nakase.

Tracheal cytotoxin displaces serotonin binding to respiratory epithelial cells. J.L. Collier, W.E. Goldman.

Molecular structural requirements for tracheal cytotoxin function. K.M. Erwin, J.L. Collier, G.R. Marshall, W.E. Goldman.

A comparative study of dermonocrotic toxin activities of serotype D *Pasteurella multocida* and the genus *Bordetella*. Kimberly E. Walker, Alison A. Weiss.

The location of filamentous hemagglutinin and pertussis toxin antigens of *Bordetella pertussis* by immunoelectron microscopy. Hideo Watanabe, Shuichi Kanesaki, Yukio Shukuda, Hiroshi Mayahara.

Adherence of *Bordetella pertussis* on the HeLa cell surface. Tuen-Yee Wong, Adriana Stefancic.

Filamentous hemagglutinin and the 69-kDa protein, pertactin, promote adherence of *Bordetella pertussis* to epithelial cells and macrophages. A. Bhargava, E. Leininger. M. Roberts, Z.M. Li, S. Stibitz, I. Charles, N. Fairweather, P. Novotny, C.R. Manclark, M.J. Brennan.

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